HODGKIN'S DISEASE AND ALLIED DISORDERS



Hodgkin's granuloma Dr Hodgkin's case #2 Guy's Hospital #1523 1828.

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Introduction

THE TITLE *Hodgkin's Disease and Allied Disorders* has been chosen after careful consideration because it seems best to embrace the various pathologic entities that are the subjects of this monograph, namely, Hodgkin's disease, reticulum cell sarcoma, giant follicle lymphoma, lymphocytoma, lymphosarcoma, plasmocytoma, and endothelioma.

The term 'lymphoma' or 'malignant lymphoma' is not infrequently used to cover this group of conditions. This we believe to be a mistake (we ourselves have so erred), for these terms connote to some a specific disease, while to others they are vague and meaningless. We further believe that it is wrong and misleading to group all these conditions under one general term (as is so often done), just as it would be wrong to include, without further definition, under 'pneumonia' those cases of pneumonia due to viruses, those due to pneumococci and other bacteria, and those due to unknown agents. Fortunately, we can properly speak of 'the pneumonias.' We cannot, in our opinion, speak with equal propriety and clarity of 'the lymphomas.'

We do not intend to discuss the many other diseases that may involve lymphoid tissue, such as tuberculosis, sarcoid, or infectious mononucleosis. Some of these diseases may in their incipiency be difficult to distinguish from those considered in this monograph. However, their clinical picture, their course, and their prognosis are entirely different from Hodgkin's disease and allied disorders.

On the other hand, we do not propose to discuss the leukemias except in so far as they are directly connected with some of the diseases considered. The leukemias as such should be treated by themselves and excellent monographs on their various aspects are readily available.

No attempt has been made to refer to all available literature. Much of it is extremely confusing and indeed misleading, even to those particularly interested in this field, and, with the exception of the later contributions, a complete bibliography will be found in the monumental work of Henke Lubarsch.

Only one new term has been introduced, namely, 'Hodgkin's paragranuloma.' This condition, as will be shown, is frequently, although not invariably, a precursor to the more serious Hodgkin's granuloma.

The chapter dealing with x ray therapy is deliberately brief and noncommittal so far as actual dosages are concerned, for this matter is a highly technical one and, while we believe that the radiologist, the pathologist, and the internist should co-operate, we believe equally strongly that the details of x ray therapy should be left to the radiologist in charge of the actual therapy.

The study is based largely on material collected over a period of years from

the Boston City Hospital, the Collis P. Huntington Memorial Hospital, the Pondville Hospital (Massachusetts Department of Public Health), and our own private practice From the Children's Hospital in Boston we have added certain data with the permission of Dr W. E Ladd

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Boston
June 1947

HODGKIN'S DISEASE AND ALLIED DISORDERS

I

Hodgkin's Disease

1. HISTORY, ETIOLOGY, INCIDENCE

It is our purpose to give a brief account of the clinical picture of Hodgkin's disease, its treatment and its prognosis, together with such descriptions of the pathology of the condition in its various forms as seem necessary for an understanding of the limits of the entity included under this title

No attempt will be made to cover exhaustively the extensive and often confusing literature For a more complete bibliography, the reader is referred to the admirable review of Wallhauser and the work of Sternberg (1936)

Classification

In our opinion, Hodgkin's disease can and should be divided into three types – paragranuloma, granuloma, and sarcoma We believe that it is essential to recognize the existence of these three forms of the disease, for the pathologic picture, the clinical aspects, and the prognosis differ materially with each We hope to be able to show that this subdivision is of practical value to the clinician as well as to the pathologist No originality is claimed for such a classification, but it is our belief that it is not so widely recognized and utilized as it should be

The Germans include in their *Granulomatose* the granulomatous form and also some cases that we classify as sarcomatous Sternberg did not recognize the paragranuloma type and denied the existence of the sarcoma Ewing, however, postulated the occurrence of the latter arising from the granulomatous type

It should become clear, as this presentation of the pathologic and clinical features of the three types of the disease proceeds, that any description that includes all three as a single form of the condition must, of necessity, be inaccurate and of little practical value

Paragranuloma, granuloma, and sarcoma are included as three different types of Hodgkin's disease on the basis of two features The first is the presence in each of the so-called Reed-Sternberg cells We believe strongly that the diagnosis of Hodgkin's disease cannot be made in their absence Some authors describe what they term an early form of the disease, characterized by hyperplasia and hypertrophy of the reticulum and endothelial cells, without the presence of Reed–Sternberg cells In our opinion, such a diagnosis is not justified The second feature is the transformation, with the passage of time, of one type of the disease into another Thus, a patient may be stricken with what is proved by biopsy to be Hodgkin's paragranuloma, and months or even years later a second biopsy may reveal the presence of Hodgkin's granuloma Similarly, a granuloma may become

a sarcoma, or, much more rarely, the two forms are found coexisting in the same patient or, exceptionally, in the same node It should be emphasized in this connection that we have never encountered what might be termed a reverse transformation — that is, a Hodgkin's sarcoma reverting to a granuloma, or a granuloma regressing to a paragranuloma What we regard as the most benign form may and frequently does progress into the more malignant one The reverse never occurs

Historical Summary

Hodgkin's paragranuloma Hodgkin's paragranuloma first appeared in the literature under the unfortunate name 'early Hodgkin's' (Jackson) To be sure, this type is often early in the sense that it is, in many cases, a precursor of the more rapidly advancing granulomatous type, yet patients with Hodgkin's paragranuloma may live unembarrassed by their disease — if the pathologic picture does not change — for many years One patient (L C, S36-1256) is living and active thirty nine years after the first proved lymph node involvement, although the condition, as shown by successive biopsies, is still present The term 'early' under such circumstances is hardly an apt one Therefore the designation 'paragranuloma' has been introduced, the prefix indicating 'in close relation to' So far as we are aware, this exact designation has not been used elsewhere in the literature

Hodgkin's granuloma. We confine the term 'Hodgkin's granuloma' to the type familiar to all There is probably no other disease to which so many different names have been applied Wallhauser in his excellent review mentions more than fifty terms that have appeared Such a state of affairs renders a study of the literature, and particularly the older literature, extremely difficult and has unquestionably caused much confusion and misunderstanding in the minds of students of the disease The multiplicity of terminology is undoubtedly due to a lack of knowledge of the true nature of the condition

In 1865, Wilks suggested the name 'Hodgkin's disease' In addition to this term the most widely used and most generally accepted are lymphadenoma (Wunderlich), malignant lymphoma (Billroth), malignant granuloma (Benda), lymphogranuloma (Grosz), and scirrhous lymphoblastoma (Mallory) The *Index Medicus* used the term 'Hodgkin's disease,' whereas the *Quarterly Cumulative Index* listed the disease under 'lymphogranuloma' until 1941, when the term Hodgkin's disease' was reinstated

Few diseases have been given a clear-cut, comprehensive, and definite description by the investigators who first brought them to the attention of the medical profession Hodgkin's granuloma is no exception to this rule In 1832, Thomas Hodgkin described 7 cases with generalized lymphadenopathy and splenomegaly and noted that 'as far as could be ascertained from observation, or from what could be collected from the history of the cases, this enlargement of the glands appeared to be a primitive affection of those bodies, rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed texture through the medium of their inferent vessels' Hodgkin was further arrested by the state of the spleen which in all but one case was found more or

less diseased and in some cases was 'thickly pervaded with defined bodies of various sizes in structure resembling that of the diseased glands' He concluded that there was 'a close connection between the derangement of the glands and that of the spleen,' and he believed that the latter was 'a posterior effect and on this account may not always have been produced, when that of the glands or some other disease carried off the patient'

It is true that among Hodgkin's original cases there were probably but 3, at most 4, of the condition that now bears his name (Fox), and it has been the custom, from time to time, to belittle his contribution as uninspired and uninspiring It would seem juster to acknowledge that the nineteenth century physician recognized a disease entity at a time when pathology was in its infancy and when the microscopic examination of tissues was virtually unknown

Hodgkin's contribution seemed, nevertheless, to have been lost sight of until 1856, when Sir Samuel Wilks described a number of cases of 'lardaceous disease' He wrote with chivalrous honesty that on the completion of his paper he had chanced to meet with the observations of Hodgkin in the seventeenth volume of the *Medico-Chirurgical Transactions*, and lamented that 'Doctor Hodgkin did not affix a distinctive name to the disease' But, even so, it was not until 1865 that Wilks really clarified the clinical entity by describing 15 cases, '13 of which resembled in all particulars the first 4 [*sic*] which Mr Hodgkin first brought under the notice of the profession' At that time, Wilks apparently recognized even more clearly than did Hodgkin that among conditions affecting 'the lymphatic glands and the spleen' there was a distinct and separate pathologic entity, for he wrote 'This disease of Hodgkin is clearly separable from lardaceous disease, from cancer, and tubercle, although these affections may bear a relation to one another It is, however, as much a disease *sui generis* as any other and deserves a description of its own' Wilks noted the generalized lymphadenopathy, the splenomegaly, and the not infrequent involvement of the liver, kidneys, and lungs He drew particular attention to the 'remarkable anemia,' and it is clear that he separated the condition sharply from the leukemias

Knowledge of the condition was, however, still in a nebulous state, and it was not until 1878 that Greenfield described, in so far as he was able with the equipment of his day, not only the gross but also the microscopic appearance of the involved tissues Greenfield evidently used the terms 'Hodgkin's disease' and 'lymphadenoma' interchangeably, for concerning his second case, one of 'lymphadenoma,' he wrote, 'On section, the spleen presented very typically the condition usually found in Hodgkin's disease' 'In all five cases,' he added, 'the change in the gland was of the same kind It consisted essentially in a sort of chronic inflammation involving especially the fibrous stroma of the glands which became thickened and gradually obliterated entirely the interstices so that the gland became a mass of dense, tough fibrous tissue with little or no adenoid structure In the early stages, there was some general enlargement of the glands the fibrous stroma appeared coarser and there were a large number of multinucleated cells adherent to the trabeculae' In a similar manner, he reported 'The normal structure of the spleen in the affected parts appears to be entirely lost, it is everywhere traversed by irregular broad bands of fibrous tissue,

which in many parts looks as much like sections of tendons as anything At their edges, and in small places left between them are seen cells of various sizes massed together, a good many large multinucleated cells being amongst them'

Greenfield, too, distinguished Hodgkin's disease from leukemia 'In all five cases of typical lymphadenoma here shown,' he wrote, 'the blood was examined and no increase whatever of leucocytes observed, so that as far as my own experience *in ten cases is concerned, I have no* ground for believing in the presence of leucocythemia in typical cases of Hodgkin s disease'

Thus Greenfield in 1878 first brought to the attention of pathologists the increase of fibrous tissue and the presence of multinucleated *giant cells He further* noted that 'clinically the disease, when well marked, exhibits an irregular febrile course periods of latency and progress, a marked and peculiar anemia'

A further chapter in the histopathology of the disease was written by Goldmann, who in 1892 noted the frequent presence of eosinophils in the diseased tissue In 1898, Sternberg discussed at great length what he believed at that time to be a peculiar form of tuberculosis masquerading as 'pseudoleukemia,' and described in detail the characteristic giant cells and the areas of necrosis Thus, by 1898 both the main clinical features and the chief histologic findings had been elucidated and Hodgkin's disease had emerged as a definite and clearly *recognizable entity*

It remained for Reed in 1902 and Simmons in 1903 to place the knowledge of the condition on a still firmer footing by their accurate and careful studies of the pathological findings in conjunction with the clinical histories Reed concluded her study in 1902 by saying

> We believe, then from the descriptions in the literature and the findings in [illegible]
>
> tion of lymphoid cells and characteristic giant cells and a gradual [illegible] connective tissue, resulting in fibrosis and, in most of the specimens, in the presence of great numbers of eosinophils

It must, perhaps, remain a matter of personal choice whose name should be assigned to *the ever-present and diagnostic giant cells Without doubt, they were* recognized by Greenfield in 1878, and their characteristics were fully depicted by Sternberg in 1898 but Sternberg had the misfortune to study a series of cases of Hodgkin's disease combined with active tuberculosis, and only in his later years did he give up the idea that he was dealing with a peculiar form of tuberculosis Perhaps the greatest credit should go to Reed, who described the cells even more accurately than did Sternberg and who recognized clearly that they were an integral part of the disease described by Hodgkin seventy years before

Hodgkin's sarcoma. The concept that Hodgkin's granuloma may become transformed into Hodgkin's *sarcoma is sometimes traced to* Yamasaki but *the* histologic descriptions of the 'tumor' from his 2 cases in no way substantiate his claim which is indeed supported solely by the title of his paper Welch reported a case from which a biopsy six months before death showed Hodgkin's gran-

uloma. Autopsy showed widespread involvement by what may well have been a sarcoma developing from a granuloma Ewing wrote in 1928 'The transformation of Hodgkin's granuloma into a sarcomatous process occurs in a certain proportion of cases,' and added 'The structure varies from a close counterpart of Hodgkin's granuloma to a tissue composed exclusively of large round cells with faintly staining cytoplasm and moderately chromatic vesicular nuclei Large round giant cells with multiple or multilobed nuclei predominate'

Comparatively few authors refer to this, the most fulminating, form of Hodgkin's disease, although, as Ewing rightly points out, 'Many cases described in the literature as lymphosarcoma are probably of this nature'

Nature of the Disease

Hodgkin's paragranuloma

Hodgkin's paragranuloma bears little or no resemblance to a true tumor, either in its histologic picture or its clinical course The often scattered, isolated Reed-Sternberg cells, the lymphocytic infiltration with or without destruction of the lymph follicles, and the complete lack of invasiveness all bespeak an infectious process, as do the comparatively benign course and the fact that in almost all cases the disease starts in the lymph nodes of the neck, to which the causative agent may have gained access through the pharynx It is not improbable that the paragranulomatous form bears to the granulomatous type of the disease the same relation that a primary tubercle does to fibrocaseous tuberculosis

Hodgkin's granuloma

As might be expected from the varied terminology already referred to, opinions concerning the nature of the granulomatous type of the disease are equally at variance Billroth and Benda were firmly convinced that it was a malignant neoplasm In this country, this concept has been upheld by Warthin, Mallory, and others The contrary view — namely, that the condition is an inflammatory or infectious disease and not a neoplasm — has been advocated by Sternberg (1936), Fraenkel, Terplan, Mittelbach, and many other workers, both abroad and in this country

Still another group believes that the granulomatous type represents a combination of an inflammatory and a neoplastic process Thus Chevalier and Bernard have suggested that it may be an inflammatory reaction due to a virus and that it later changes into a blastoma, as do the infectious epitheliomas

As has been said above, the fact that the Reed-Sternberg cells are frequently scattered, isolated and often separated widely by cells of other types favors an inflammatory process rather than a neoplasm, for certainly in no true tumor does this condition obtain On the clinical side, the irregular bouts of fever, seldom absent in the more advanced stages and often seen to a less degree early in the course and more especially the relapsing type commonly called 'Pel-Ebstein fever,' the marked anemia in absence of bleeding or widespread invasion of the marrow, the polymorphonuclear leukocytosis, and the prominent and persistent tachycardia are all more characteristic of an infectious process than of a tumor.

HODGKIN S SARCOMA

Hodgkin s sarcoma has in our opinion all the characteristics of a true neoplasm The uniformity of the cellular constituents the aggressive invasive nature of the process the extremely short duration of life and the not uncommon finding of a large destructive tumor with comparatively few metastases all favor this concept So also does the fact that the disease is commonest in the sixth and seventh decades and is extremely rare below the age of thirty This view however is contrary to that held by many workers such as Kaufmann and Sternberg (1936) who maintain that this cellular type is merely a variant of the granulomatous form and is of the same basic nature As already noted however Ewing speaks of sarcomatous transformation in certain cases of Hodgkin s disease and we have made similar observations in our own cases

ETIOLOGY

If our concept of the disease is correct the etiology of the paragranulomatous form is identical to that of the granulomatous The granulomatous form is not brought into existence at the time owing either to relative immunity on the part of the host or to comparative lack of virulence on the part of the exciting agent

HISTORICAL SUMMARY

Many authors have emphasized the importance of the tubercle bacillus as the etiologic agent in Hodgkin s granuloma Sternberg (1898) originally described the lesion as an atypical form of tuberculosis (8 out of 13 of Sternberg s original series of cases were complicated by definite tuberculosis) Lichtenstein claimed to have produced Hodgkin s granuloma in guinea pigs by the injection of material from human cases and of tubercle bacilli Fraenkel and Much demonstrated antiformin resistant gram positive granules in granulomatous tissue that showed no demonstrable evidence of tuberculosis Furthermore by injections of large amounts of antiformin treated material they succeeded in producing not only tuberculosis but also lesions that in their opinion resembled those of Hodgkin s granuloma

L Esperance claimed to have shown that the etiologic agent was an avian strain of tubercle bacilli Her work could not be confirmed by other workers including van Rooyen (1933) Branch and ourselves

Perhaps an equal number of investigators have denied the etiologic role of tuberculosis in the production of Hodgkin s granuloma Both Reed and Longcope whose publications amplified Sternberg s original description of the disease denied the identity of Hodgkin s granuloma with tuberculosis Terplan and Mittelbach as a result of their own experiments and a review of the literature held the same view They believed that in those cases in which positive evidence for tuberculosis was obtained the tubercle bacillus was either a secondary or coincident invader and was in no way causative of the Hodgkin s disease Furthermore these authors were not convinced that Hodgkin s granuloma had ever been produced in experimental animals Uddstromer in his study of 548 cases

of Hodgkin's granuloma likewise found no support for the thesis that tuberculosis is the causative agent

The literature on this particular aspect of the problem is exceedingly extensive, and the reader who wishes further details is referred to the reviews by Wallhauser, Sternberg (1936), Terplan and Mittelbach, and Simonds

The tuberculin test has been employed by various investigators in an attempt to prove or disprove a direct relation between the two diseases Cases of Hodgkin's granuloma have almost uniformly been anergic, reacting if at all, only to low dilutions — 1 10 or 1 100, rarely 1 1000 The test often becomes positive frequently strongly so, after effective x ray therapy

It should be emphasized that Hodgkin's granuloma is frequently complicated by tuberculosis According to Ziegler and other workers, this occurs in 15 to 25 per cent of cases In our own series, we found coexistent active tuberculosis in 20 per cent The fact that one may find in the same patient or even in the same organ both Hodgkin's granuloma and tuberculosis has seemed to us to indicate the lack of identity of the two diseases, for it appears highly improbable, if not impossible, that a host should react in two entirely distinct ways to the same micro organism Furthermore, if the tubercle bacillus is actually the cause of Hodgkin's granuloma, the disease should be found more commonly in persons suffering from proved tuberculosis than in those free of the disease Such does not appear to be the case Medlar found Hodgkin's disease in only 0 3 per cent of patients who had tuberculosis and were followed until death at the Metropolitan Life Insurance Company Sanatorium, and of 2297 cases of tuberculosis [illegible]

careful analysis of the situation in Sweden found that Hodgkin's disease was less common in areas in which the tuberculosis rate was high than in those in which it was low

Various diphtheroid bacilli have also been claimed as the etiologic agent by a number of investigators Among these may be mentioned DeNegri and Mieremet, Bunting and Yates, Bloomfield, and Torrey Bunting and Yates named their organism *Bacterium hodgkinii* and claimed that injections into animals produced Hodgkin's granuloma Others have not been able to confirm their work, however, and numerous investigators have found diphtheroid bacilli in lymph nodes from a variety of other conditions, such as lymphosarcoma, metastatic carcinoma, and tuberculosis It is now generally held that such diphtheroids as have been identified are not of etiologic importance

It has also been claimed by Kofoid that amebas are the cause of the disease There has been no confirmation of this claim

Gordon (1932, 1933) in England found that material from Hodgkin's granuloma injected intracerebrally into rabbits produced paralysis that usually resulted in death Negative results were obtained with the material from cases of carcinoma, sarcoma, and with other pathologic tissues Gordon concluded that this was a satisfactory diagnostic test, and he believed, furthermore, that the disease was due to a specific pathogenic agent, probably a virus, although he

was unable to transmit it from rabbit to rabbit Van Rooyen (1933 1934) confirmed Gordon's results in so far as the test was concerned In collaboration with Turner, we demonstrated that the Gordon test is apparently entirely dependent on the presence of eosinophils and is in no way specific for Hodgkin's disease Our work has been confirmed by Edward, King and McNaught

Another group of workers believes that Hodgkin s granuloma is a special — by some considered allergic — type of reaction of the tissues to any of the usual pyogenic organisms and that the disease, therefore, has no single etiologic agent

The latest contributions of note on the subject of etiology are those of Parsons and Poston and Wise and Poston In the latter paper it is reported that cultures of lymph nodes from 14 consecutive cases of proved Hodgkin's granuloma yielded positive cultures for organisms of the Brucella group They further found that such patients were anergic to abortin Cultures from 67 cases with diseases of lymph nodes other than Hodgkin's disease with one exception yielded negative results It is as yet too early to pass final judgment on the significance of these findings To date, we have been unable to confirm them

Twort in an extensive study of the etiology of Hodgkin's granuloma using a great variety of cultural methods obtained entirely negative results

BACTERIOLOGIC STUDIES

For three years, we cultured lymph nodes removed aseptically at surgical operations on an egg medium suitable for growing tubercle bacilli Approximately seventy five nodes from patients with a variety of diseases were so cultured In no case did material from a Hodgkin s granuloma yield a positive culture for *Mycobacterium tuberculosis,* whereas material from tuberculous nodes gave uniformly satisfactory growths of the organism It should be noted that in 3 cases of Hodgkin's granuloma, smears made from the apparently negative surfaces of the inoculated slants of egg medium showed acid fast bacilli These would not grow in subculture, and their nature is entirely obscure

In addition to the egg medium used we also cultured the last fourteen nodes of this first series in dextrose ascitic fluid broth sealed with vaseline, as well as in ascitic fluid broth and brain broth and on blood agar Four of the nodes so cultured three from cases of Hodgkin's granuloma and one from a case of Hodgkin s paragranuloma yielded a growth of a small gram positive, strictly anaerobic, gas forming bacillus In smears of cultures the organisms occurred in clumps and chains Because of this finding and the negative results of our efforts to demonstrate the tubercle bacillus we discontinued our cultures for the latter and concentrated on culturing for this anaerobic bacillus For this purpose, we used chopped meat broth sealed with vaseline, a medium that we had found favorable for its growth

Eighty one lymph nodes were cultured in this medium The organism was obtained from a considerable number of cases of Hodgkin's disease It was, however, cultured also from cases with other forms of lymphoma and from nodes involved by carcinoma tuberculosis and chronic inflammation A positive blood culture for this organism was obtained from a febrile case of Hodgkin's granuloma (J A S36–4092) at the height of the fever, whereas cultures were negative

when the temperature was normal A positive blood culture of a similar organism was, however, likewise obtained from a patient who, so far as was known, did not have the disease

Attempts to demonstrate a relation of this organism to Hodgkin's disease by means of agglutination and skin tests failed The bacillus was not pathogenic for the usual laboratory animals — rabbits, guinea pigs, and mice Its significance, therefore, remains doubtful

A series of nodes were also cultured in sheep's blood broth and on blood agar plates and slants, the latter being incubated under normal atmospheric conditions and under increased carbon dioxide tension (10 per cent) The results were consistently negative except for the rare presence of a readily recognized contaminant, such as a staphylococcus It should be mentioned here in connection with our technical procedure that such contaminations were uncommon

ANIMAL INOCULATIONS

Portions of the lymph nodes used for culturing for tubercle bacilli were also injected into rabbits, guinea pigs, and pigeons The rabbits were inoculated intravenously, subcutaneously, and, rarely, intracerebrally, the guinea pigs intraperitoneally and subcutaneously, and the pigeons intravenously and intraperitoneally All the animals were kept for from several months up to one and a half years before being killed and autopsied In the entire group of animals inoculated with material from Hodgkin s granuloma, only one guinea pig showed tuberculosis, the organism proving to be a bovine strain This node was from a child aged ten years (M G, S28–1801) and microscopically showed no evidence of tuberculosis but rather what appeared to be an uncomplicated picture of Hodgkin's granuloma Nodes from the other forms of Hodgkin's disease and other types of lymphoma, as well as carcinomatous nodes and inflammatory nodes, gave negative results As was to be expected all material from cases of tuberculosis produced that disease in the animals

TUBERCULIN REACTIONS

As reported in a previous paper (Parker, Jackson, FitzHugh, and Spies), we carried out a series of intracutaneous tuberculin reactions using both human and avian tuberculin The patients so tested comprised sufferers from a variety of diseases besides Hodgkin's granuloma and included a number known to have active tuberculosis The patients with Hodgkin's granuloma showed a definite anergy to both types of tuberculin The significance of this anergy is entirely obscure, but it suggests that tuberculosis is not the cause of Hodgkin's granuloma, furthermore, if an untreated case of proved Hodgkin's granuloma reacts positively to high dilutions of tuberculin, this indicates that the patient also has active tuberculosis

In considering all the evidence at hand from reports in the literature and from our own work, we are forced to conclude that the etiology of Hodgkin's granuloma has yet to be discovered

INCIDENCE

Hodgkin's granuloma is, fortunately, an uncommon disease. Uddstromer found only 548 cases in the whole of Sweden between 1915 and 1931, an incidence of 0.054 cases per 10,000 living persons as based on the average population of the country during that period. All cases were proved by biopsy or autopsy, and all tissue was examined by the author himself. Among 8485 general autopsies, Symmers found 14 cases of Hodgkin's disease, and in Barron's 7253 autopsies there were 24 cases. The combined incidence as estimated from these two latter series is 0.23 per cent. Ciechanowski found an incidence of 0.33 per cent in 60,000 autopsies.

In our own series of 259 proved cases,* the total available figures must be broken down, for many cases were admitted to the Collis P. Huntington Memorial Hospital or the Pondville Hospital, two institutions that are devoted primarily to the care of patients with one or another form of malignant disease and likely, therefore, to have a disproportionately large number of cases of Hodgkin's disease in their wards. A juster estimate of the incidence of the disease, so far as our own experience is concerned, may be derived from the figures at the Boston City Hospital. At this institution, there were 18,668 autopsies from 1897 to 1946, and among these 63 showed Hodgkin's granuloma, an incidence closely approximating that of the combined figures of Symmers and Barron referred to above. It should be emphasized that all our autopsy and biopsy material of whatever date has been comprehensively reviewed by us personally during the last three years, so that in all cases the diagnosis has been made in the light of the most recent histologic knowledge.

We may tentatively conclude that Hodgkin's granuloma accounts for approximately 0.25 per cent of deaths in a general hospital.

Uddstromer found the condition six times as common in 1931 as in 1915. He was hesitant in saying that there had been an actual increased rate. Our data do not support the view that the disease is on the increase.

AGE AND SEX

Hodgkin's paragranuloma. The age incidence of Hodgkin's paragranuloma is shown in Table 1; it roughly parallels that of the granulomatous form (Table 2). Of 41 patients, 30, or 73 per cent, were males.

Hodgkin's granuloma. Although it has been repeatedly stated that Hodgkin's granuloma principally affects young adults, it is of the greatest importance to recognize that the condition may occur at any age. In the literature, there is no consensus concerning the decade in which it is most commonly seen, and some confusion has arisen from the facts that certain authors derive the age incidence from the date of the first symptoms, that others have recorded their cases accord-

* Only those cases have been included from which we had, at the time of study, satisfactorily stained tissue. Some of these have been omitted from subsequent tables because

TABLE 1 *Age at Onset of Hodgkin s Paragranuloma*

AGE yr	NO OF CASES	PER CENT
0–9	2	5
10–19	6	15
20–29	9	22
30–39	7	17
40–49	5	12
50–59	5	12
60–69	6	15
70–79	1	3
Total	41	

ing to the age at death and that still others have contented themselves by saying that the disease occurred in certain decades

Uddstromer who carefully dated his cases from the first symptom that could properly be attributed to the disease found that the condition was commonest in the third decade but his figures (Table 2) indicate clearly that no age group is spared

On the other hand in Longcopes series of 109 cases 19 per cent occurred in the first decade of life and of Smiths 138 cases over 12 per cent were under the age of ten In sharp contrast Sternberg (1936) reports 29 per cent of his autopsied cases as falling in the sixth decade and 25 per cent in the seventh and Priesel and Winkelbauer report a case of a child who apparently had the disease

TABLE 2 *Age at Onset of Hodgkin s Granuloma (Uddstromer — 536 cases)*

AGE yr	PER CENT
0–9	6
10–19	9
20–29	24
30–39	19
40–49	14
50–59	14
60–69	11
70–79	3

at birth and died at the age of four months It is thus apparent from a study of the literature that no age is spared and that the condition is found with reasonable constancy throughout the first seven decades of life Our own experience confirms this view for our cases are distributed quite evenly from earliest childhood to the age of seventy (Table 3)

Wallhauser believed that the number of cases developing during the period of puberty was surprisingly and significantly small since he found that of 33 cases in patients under fifteen only 2 occurred between the ages of twelve and fourteen Similarly in Uddstromers series of 57 cases with onset under the age of sixteen only 6 came down with the disease in the period of puberty and of our own 43 patients under the age of sixteen only 6 all boys, were first stricken between the ages of twelve and fourteen As Uddstromer points out however the num

TABLE 3 *Age at Onset of Hodgkin s Granuloma*

AGE yr	NO OF CASES	PER CENT
0–9	27	11
10–19	32	14
20–29	41	17
30–39	35	14
40–49	37	16
50–59	32	14
60–69	25	11
70–79	7	2
80–89	1	1
Total	237	

ber of cases in the childhood period is so small that one must be cautious be fore drawing any broad conclusions on this particular point and furthermore the age at which puberty begins varies over rather wide limits in different lati tudes and in various races

For the present the most important consideration is the undeniable fact that Hodgkin s granuloma may occur at any age although it appears to be uncommon in infancy and in extreme old age

There is general agreement that Hodgkin s granuloma is commoner in males than in females Nearly 70 per cent of the patients in the 1447 cases collected from the literature by Wallhauser and 61 per cent of Uddstromer s 548 patients were males This preponderance becomes even more marked in children for 91 per cent of Uddstromer s and 94 per cent of Smith s patients under the age of ten were males In our own series of 237 patients 70 per cent were males and almost precisely this proportion was maintained in the childhood group There does not appear to be any adequate explanation for this sex difference

TABLE 4 *Age at Onset of Hodgkin s Sarcoma*

AGE yr	NO OF CASES	PER CENT
0–9	0	0
10–19	0	0
20–29	2	4
30–39	8	16
40–49	6	12
50–59	14	27
60–69	14	27
70–79	7	14
Total	51	

It is our belief that Hodgkin s granuloma occurs more frequently in members of the same family than can be accounted for by chance alone

We have recently seen a 30 year-old man with proved Hodgkin s granuloma who had two brothers and one sister with the same disease We have twice seen Hodgkin s granuloma and lymphatic leukemia in the same patient We know of one patient who had carcinoma mycosis fungoides and Hodgkin s granuloma

It would appear that the hematopoietic and lymphatic tissues in the same in

dividual or in closely related siblings are more prone to be subject to the neoplastic or neoplastic like diseases considered in this monograph

Hodgkin's sarcoma Hodgkin's sarcoma occurs chiefly in the middle aged or elderly (Table 4) Eighty per cent of our 51 patients were over forty years of age In no case have we seen a patient with primary Hodgkin's sarcoma — that is not preceded by Hodgkin's granuloma — under twenty years of age Twenty six or 51 per cent of our patients were men It is apparent therefore, that both the age and the sex distribution differ sharply from those of Hodgkin's granuloma and paragranuloma

Summary

Hodgkin's disease in our opinion should be subdivided into the paragranulomatous the granulomatous and the sarcomatous type The nature etiology and incidence of these three varieties have been discussed their pathologic and clinical pictures and their treatment will be considered in subsequent chapters

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2 PATHOLOGY

This section will discuss the gross and microscopic features of the three types of Hodgkin's disease the apparent site of origin in each, and the extent to which each form involves the various organs of the body Without some knowledge of the gross pathology and the distribution of the lesions, one cannot hope to have a clear understanding of the clinical aspects of the disease

Hodgkin's Paragranuloma

Hodgkin's paragranuloma appears to be a disease essentially of the lymph nodes Those involved are most frequently found in the neck and are usually few in number discrete of rubbery consistence and not attached to the surrounding tissue (Table 1) They are rarely more than 3 cm in diameter and

Table 1 *Apparent Primary Site of Disease in Cases of Hodgkin's Paragranuloma*

	No of cases
Cervical lymph nodes	25
Inguinal lymph nodes	3
Axillary lymph nodes	1
Uncertain	2
Total	31

on cut section are yellowish gray There is no evidence of softening or necrosis, and the capsule is intact

On microscopic examination the normal structure of the lymph node as a whole is occasionally unaffected more commonly it is partly or entirely lost In some cases the lymph follicles are preserved and show only varying degrees and types of cellular activity in others they are partly or completely obliterated The peripheral sinus may be clearly outlined or it may be compressed by the follicles or obscured by cellular infiltration

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of the disease. The initial biopsy specimens from these two cases were indistinguishable In the first case, the type of lesion did not alter over a period of twenty six years, and the patient was alive and active thirty nine years after the initial lymphadenopathy had been noted In the second case, on the other hand, the histologic picture changed with considerable rapidity and death shortly ensued A third patient (Jo H) had a large mass of nodes dissected from the neck in 1920 He remained active and in apparent good health until 1943, when he returned with a large mediastinal mass and a few lymph nodes in the neck. These proved on biopsy to be Hodgkin's granuloma In 3 other cases, Hodgkin's granuloma developed, as proved by autopsy Four patients died of unrelated causes, such as carcinoma or tuberculosis, and 5 died from causes unknown Unfortunately, no autopsy was obtained in any of the latter cases Fourteen patients are alive and active, although some still show evidence of their disease

It should be emphasized that, so long as the pathologic process remains unaltered, the prognosis is relatively good but in certain cases Hodgkin's granuloma develops, and the prognosis then becomes that of the latter condition

If the pathologic process remains that of Hodgkin's paragranuloma, involvement of the internal organs appears to be rare In 4 cases, the mediastinal nodes became involved Three of these patients are still alive, and 1 died of pulmonary tuberculosis In 2 cases, the spleen became definitely enlarged Each of these patients died at home of unknown causes In 3 cases, both the mediastinal nodes and spleen became involved. All these patients have died There were no autopsies

We have had three autopsies on cases of Hodgkin's paragranuloma The organs and tissues involved are shown in Table 2

TABLE 2 *Organs involved in 3 Cases of Hodgkin's Paragranuloma Autopsies*

Lymph nodes	3
Spleen lung liver, kidney, bone marrow	1 each

One case had, in addition, acute, generalized miliary tuberculosis

Hodgkin's Granuloma

The granulomatous process may involve isolated groups of nodes in certain regions, or the process may be widespread In our series of cases, the lymph nodes were implicated to some extent in every case Cases have been reported, however, in which the disease was confined to a single organ with no lymph-node involvement, such as the 2 cases mentioned by Sternberg (1936) in which the spleen alone was diseased.

From autopsy studies of 63 cases, it is clear that the retroperitoneal and para aortic lymph nodes were the most frequent primary site of the disease, followed by other lymph nodes and the stomach or intestines (Table 3) This is in sharp contrast to the clinical observations, from which it appears that the cervical nodes were the primary site in an overwhelming percentage of the cases. It is probable that the favorable response of the more superficial nodes to x-ray

The diagnosis is based on the presence, within the involved nodes, of Reed-Sternberg cells, which may be few or numerous They occur especially in the pulp, more rarely they are seen in the lymph follicles The large cells with multi lobed or, more rarely, multiple nuclei and prominent nucleoli are indistinguish able from those found in the other forms of Hodgkin's disease The cytoplasm is fairly abundant and tends to be amphophilic Mitotic figures in the Reed-Sternberg cells of this form of Hodgkin's disease are not numerous

The predominant cell of Hodgkin's paragranuloma is, however, the adult lymphocyte In cases in which the lymph follicles have been obliterated the diffuse infiltration of the nodes by lymphocytes may be so great that an erroneous diagnosis of lymphocytoma is easily made Buried within this mass of lympho cytes are found, nevertheless, the typical Reed-Sternberg cell, for which a careful search must be made Reticulum cells, often containing phagocyted debris, are present in varying numbers In some cases they occur as focal aggregates resembling the lesions of Boeck's sarcoid Plasma cells are not uncommonly seen and may be numerous Eosinophils are sometimes present, but never in such quantities as in Hodgkin's granuloma

The pathologic process never invades the capsule, although there may be an infiltration of this structure by scattered lymphocytes and plasma cells In Hodgkin's paragranuloma one never sees the necrosis, the infiltration with poly morphonuclear leukocytes, the marked eosinophilia, or the fibrosis so frequently found in Hodgkin's granuloma

The changes in the reticulum vary widely In some cases it is normal in amount, in others there is an increase in the number of fibers in the medullary cords but not in the follicles In still others the fibers are thickened, but this change is usually associated with scarring due to some independent and unrelated process

It should be pointed out that in certain cases of Hodgkin's paragranuloma the presence of fairly numerous eosinophils and fibrin is evidence that a transforma tion into the granulomatous form is impending, and transitional types of the disease occur in which it is difficult to be sure whether one is dealing with Hodgkin's paragranuloma or with Hodgkin's granuloma It may be argued that those cases of Hodgkin's paragranuloma that fail to change into Hodgkin's granuloma represent, indeed an entirely different disease. It must be remembered, however, that those that progress cannot, in their incipiency, be dis tinguished from those that do not For instance, in 1910 one of our patients (L C) had a cervical lymph node removed that showed the typical picture of Hodgkin's paragranuloma Subsequent biopsies from the neck in 1917 and 1936 showed a histologic picture indistinguishable from that seen in 1910 The patient has continued to be in good health to date On the other hand, a second patient (J H) in 1941 had a cervical lymph node removed that showed the typical histologic picture of Hodgkin's paragranuloma He was given a moderate amount of high voltage x ray treatment and continued in apparently good health until 1943 at which time he suddenly became progressively worse, with all the signs and symptoms usually associated with advanced Hodgkin's granuloma Autopsy showed extremely extensive involvement with the granulomatous type

matin occurs in heavy clumps, and large nucleoli are a prominent feature The cytoplasm, which is abundant in proportion to the nucleus, varies in its staining reaction from acidophilic to basophilic, tending to be basophilic in the younger forms In sections of tissue fixed in Zenker's fluid and stained with Mallory's phloxin methylene blue stain, the cytoplasm often appears finely reticulated

In sections stained for reticulum, the Reed–Sternberg cells often contain numerous silver positive granules In such sections these cells are often found closely applied to the reticulum fibers, and in some cases these fibers seem to pass through the cytoplasm When stained with Penfield's modification of Hortega's silver carbonate method for microglia, the Reed–Sternberg cells tend to become impregnated, as do phagocytes of mesenchymal origin, as shown by Dunning and Furth and as noted by us in unpublished studies As a general rule, there is an increase in the number of reticulum fibers, which either run between single cells or enclose groups of cells As sclerosis advances, the fibers tend to be thicker and more numerous In a completely fibrosed node, the major portion of the intercellular substance is dense collagen

Mitotic figures are not uncommon, and multiple mitoses are occasionally seen Phagocytosis by Reed–Sternberg cells is uncommon There is a strong tendency, however, for them to undergo necrobiosis Thus, in a section of Hodgkin's granuloma scattered degenerating and pyknotic Reed–Sternberg cells are frequently found, and this feature is often an aid in diagnosis when one may be in doubt whether true Reed–Sternberg cells are present

In supravital preparations, the cytoplasm has a ground glass appearance, and in some cells a delicate, finely granular rosette stained with neutral red can be seen in close proximity to the nucleus

The exact origin of the Reed–Sternberg cells has not been proved, but we agree with those workers who believe that they are derived from the sinus endothelium and from reticulum cells In favor of such an origin is their resemblance to these cells, especially when the Reed–Sternberg cells are small and mononuclear A more striking resemblance is seen in the cells of Hodgkin's sarcoma and of anaplastic reticulum cell sarcoma, in which the differential diagnosis must rest on the presence or absence of Reed–Sternberg cells It is, of course, extremely important to differentiate normal reticulum cells and Reed–Sternberg cells When the latter are large and typical, no difficulty should be encountered When, however, they are small and the nuclei are not multilobed, the differential diagnosis depends on the character of the nucleus The nucleus of a reticulum cell has finely divided, scattered chromatin and lacks a prominent nucleolus, whereas a Reed–Sternberg cell has its chromatin arranged in large masses and is characterized by one or more prominent nucleoli

Cells occasionally confused with Reed–Sternberg cells are multinucleated plasma cells, foreign body giant cells, Langhans giant cells, tumor giant cells, and megakaryocytes The last two may present great difficulties in differential diagnosis Tumor giant cells, however, rarely occur singly, as do Reed–Sternberg cells, and they are accompanied by other tumor cells characteristic of the neoplasm at hand Foreign body giant cells and Langhans cells have nuclei varying in number from several to twenty or more, and the nuclei in each of these types

TABLE 3 *Primary Site of Disease in Cases of Hodgkin's Granuloma*

SITE		NO OF CASES
Lymph nodes		57
Retroperitoneal	17	
Para aortic	17	
Mediastinal	9	
Cervical	8	
Mesenteric	6	
Gastrointestinal tract		6
Stomach	3	
Duodenum	1	
Small intestine	1	
Large intestine	1	
Total		63

therapy as well as the difficulty of recognizing during life involvement of the deeper nodes and internal organs account for this apparent discrepancy But the fact that internal lymph nodes are so frequently and primarily involved at autopsy even though they have not been suspected of being implicated during life should make the physician cautious before deciding in a given case that the disease is confined to a small number of obviously involved but comparatively localized superficial nodes

The diseased lymph nodes often occur in masses but the outlines of each can usually be made out *Their consistence may be soft or firm but with deposition* of connective tissue the nodes become increasingly harder Only rarely however do they assume the stony hardness so suggestive of carcinoma The cut surface is grayish white often with a brownish tint It may be homogeneous or may show foci of necrosis which are of varied shape and are white to yellow In our experience breaking down or softening due to Hodgkin's granuloma alone does not occur Secondary infection particularly in the groin may however give rise to abscess formation or the deposition of scar tissue to such an extent that a definitive diagnosis is impossible If feasible it is always wise to avoid the removal of a node from the groin and to choose for biopsy a lymph node in the neck or axilla provided that there is one of sufficient size and that it is *readily accessible*

The histologic picture of Hodgkin's granuloma is characterized by the presence of Reed–Sternberg cells and by its great pleomorphism The lymph nodes involved usually show complete loss of their normal architecture The germinal centers and the cords of lymphatic tissue as well as the sinuses are obliterated Extension of the process into the capsule may occur It must be remembered that in any given case the histologic picture in the nodes in different regions or even in different nodes in the same region may vary widely

The typical Reed–Sternberg cell measures from 12 to 40 microns in diameter Its shape is often irregular and cytoplasmic processes frequently extend between neighboring cells The nucleus in its most characteristic form is lobulated or multilobed *Multinucleated forms also are seen Small forms of the Reed–* Sternberg cell may occur and in these the nucleus is round or oval The chro

action on the part of the host Several patients, when first biopsied, have shown such a picture in their nodes, and their subsequent course has been relatively favorable

As is well recognized, radiation therapy produces a high degree of sclerosis In such nodes, however, even though markedly fibrosed, an occasional Reed–Sternberg cell can always be found

The lesions described above may vary considerably in the different organs or tissues of any given patient For example, some lesions present a marked inflammation with but little necrosis, others show extensive necrosis and in still others fibrosis is the outstanding feature The type of histologic picture depends presumably on such factors as the activity of the process, the age of the lesion and the reaction of the host to the causative agent

Occasionally, as Sternberg (1936) has pointed out, large amounts of lipoid are found in the reticulum cells and in giant cells of the foreign body type The significance of this phenomenon is not clear, but that it may occur must be recognized in order to avoid the error of making a diagnosis of one of the diseases of disturbed lipoid metabolism, such as Niemann–Pick's disease, and of overlooking the essential granulomatous lesion

Some authors have described another feature as not uncommon namely, amyloid formation In our experience this has been extremely rare

The granulomatous form of Hodgkin's disease is frequently associated with active tuberculosis It has been said that tuberculosis follows Hodgkin's disease like a shadow The two processes may exist side by side in the same organ, and although grossly one may be confused with the other, the histologic characteristics of each are so definite that no difficulty in distinguishing them should be encountered

The lymph nodes were involved at autopsy in every case in this series, and it is noteworthy that the involvement was usually widespread and of fairly uniform distribution (Table 4)

Aside from the generalized lymphadenopathy, almost every organ of the body,

TABLE 4 *Lymph Nodes Found to Be Involved at Autopsy in 63 Cases of Hodgkin's Granuloma*

TYPE OF NODE	NO OF CASES
Mediastinal	59
Para aortic	38
Cervical	30
Retroperitoneal	28
Mesenteric	32
Inguinal	25
Axillary	23

with the exception of the central nervous system proper, may be invaded (Table 5) This fact accounts for the extraordinarily protean clinical manifestations

The spleen is involved in a large percentage of cases In Sternberg's (1936) series it showed lesions in 80 per cent in Terplan's in 65 per cent and in Uddstromer's in 63 per cent In our series it was involved in 75 *per cent The in*

of cells are regular in shape, equal in size, and orderly in arrangement. The chromatin is finely divided, and nucleoli are not prominent. Megakaryocytes closely resemble Reed-Sternberg cells and given a single cell it is almost impossible to determine which of the two it is, although megakaryocytes do not have prominent nucleoli and their nuclei, although multilobed, are always single. The diagnosis must therefore depend on the *picture of the section as a whole*. To illustrate the difficulty of a definitive diagnosis, we refer to a nodule in the skin removed from a patient with proved myelogenous leukemia. Megakaryocytes were a prominent feature, and a number of highly competent pathologists without hesitation diagnosed the disease as Hodgkin's granuloma.

The nature and significance of the Reed-Sternberg cell is entirely obscure. It has been considered a tumor giant cell by those who consider Hodgkin's granuloma a neoplasm. In our opinion it is probably a peculiar reactive form of the reticulum cell in response to the agent causing the disease. In support of this conception is the cellular reaction to infection with *Pfeifferella mallei*, in which as is well known, a characteristic type of giant cell is seen. It is our opinion that in like manner the Reed-Sternberg cell of Hodgkin's granuloma is *the response to the unknown etiologic agent of that disease*.

The number of Reed-Sternberg cells in granulomatous nodes varies widely. In some they are few in number, in others they are numerous and may occur in groups as well as scattered. Rarely, if ever, are they so scarce as in paragranuloma.

In addition to the Reed-Sternberg cells, there are many other types of cells, and a pleomorphic picture is indeed characteristic of the disease. Lymphocytes are usually numerous. Plasma cells are almost constantly present, their number varying from a few to so many that a diagnosis of plasmocytoma may be entertained. One of the most outstanding features of the histologic picture of Hodgkin's granuloma, as first pointed out by Goldmann, is the presence of eosinophils. They are practically always present, although their number varies widely. In addition, polymorphonuclear neutrophilic leukocytes can usually be found and are particularly prominent when the inflammatory reaction is extremely active and necrosis is present. Activity on the part of the reticulum cells, as evidenced by hyperplasia and hypertrophy, is frequent sometimes with the formation of focal lesions resembling tubercles or *Boeck's sarcoid*.

In addition to the pleomorphic cellular content, two other changes are found that are characteristic of the granuloma—necrosis and fibrosis. The necrosis varies in extent from microscopic foci to large areas easily visible grossly. It is often of the infarct type, the cell outlines being preserved in the necrotic area. Polymorphonuclear leukocytes and reticulum cells may be found at the periphery of necrotic areas. Fibrin formation is common. Occasionally giant cells of the foreign body type are present. The necrotic areas are eventually organized by the ingrowth of the fibroblasts of the stroma. As the processes of necrosis and fibrosis proceed some lesions finally come to be largely composed of connective tissue often dense and sometimes hyaline in the interstices of which can be seen a few Reed-Sternberg cells. A high degree of fibrosis does not necessarily mean a long standing process on the contrary, it may represent a favorable re

disease were noted On the other hand, of the 22 livers weighing less than 1600 gm, only 5 were involved The focal, circumscribed nodules are similar to those in the spleen, or there may be grayish streaks of diseased tissue following the distribution of the portal areas If fibrosis is extensive, scars may be produced in such a manner that healed gummas are simulated Some authors have described the lesions as resembling those of cirrhosis Bile stasis, due to compression of the bile ducts by the surrounding granulomatous tissue, resulting in jaundice, does occur, but it is rare The small lesions tend to occur in the portal areas Their histologic composition and pattern are similar to those of the lesions in lymph nodes The large foci may cause compression and destruction of the surrounding liver tissue

Statistics concerning the incidence of involvement of bones in Hodgkin's granuloma are unsatisfactory because of the incompleteness of examination of the osseous system In a recent review of Hodgkin's granuloma with special reference to the involvement of the bone marrow, Steiner collected from the literature 547 autopsied cases, of which 153 (28 per cent) showed lesions of the bone marrow In his own 14 cases, he found the marrow involved in 11 (78 per cent), it should be pointed out that he examined sixty two bones in the 14 cases In our series, involvement of the bones occurred in 61 per cent of those cases in which the osseous system was examined Such a figure is, however, obviously inaccurate because of the limitations in making a thorough gross and microscopic study of the bones in each case The bones most commonly involved at autopsy, in order of their frequency, are the vertebras, especially the lower thoracic and upper lumbar, and, much more rarely, the sternum, ribs, pelvis, femur, and skull Multiple involvement is not uncommon The lesion may be confined to the marrow, or the process may invade and destroy the cortex, leading in the case of the vertebras to collapse, which, if extensive, may result in compression of the cord, although it is surprising to what extent collapse can occur without clinical symptoms Involvement of the bones may be metastatic or by extension from neighboring organs Grossly, the lesions appear as grayish to yellowish nodules that stand out against the remnants of the normal marrow *Although fibrosis of the involved marrow often occurs, osteosclerosis is rare*

Histologically, the lesions may be miliary in type, composed of typical granulomatous tissue with but little disturbance of the bony architecture, or they may be extensive, causing destruction of the bony trabeculae The process replaces the normal marrow, and at the *periphery of the process great activity on the* part of the hematopoietic tissue may be present In a specimen of marrow removed by biopsy, unless a certain degree of fibrosis is present, great difficulties may be encountered in making a definite diagnosis because of the similarity of the megakaryocytes to Reed-Sternberg cells

Verse estimated from a study of his own material and from the cases reported in the literature that approximately one third of the cases show involvement of the lungs Sternberg (1936) stated that of his 52 autopsied cases 15 (29 per cent) showed such lesions Pulmonary involvement was found in 40 per cent of our cases The lesions may be divided into three types In the first type, there appears a large, tumorlike mass, often involving the greater part of a lobe

volved organ may be normal in size or enlarged to a marked degree. The largest spleen in this series weighed 1245 gm. and the smallest 120 gm., with an average of 480 gm. The lesions appear as circumscribed focal areas gray to yellowish and varying in diameter from that of a miliary tubercle to a centimeter or more. As a rule, the lesions in each spleen are of approximately the same size. Foci of necrosis similar to those seen in lymph nodes may occur. The picture produced by the focal lesions contrasting with the red color of the uninvolved portion has led to the terms porphyry (Benda) and *Bauernwurst* (Janz) spleen.

TABLE 5. *Organs Found to Be Involved at Autopsy in 63 Cases of Hodgkin's Granuloma*

ORGAN	NO. OF CASES	
Lymph nodes		63
Spleen		48
Liver		31
Bones *		35
Vertebra	28	
Sternum	3	
Rib	3	
Ilium	2	
Femur	1	
Skull	1	
Lung		25
Pleura		10
Infiltration only	5	
Effusion only	3	
Infiltration and effusion	2	
Gastrointestinal tract		12
Stomach	5	
Small intestine	4	
Duodenum	1	
Cecum	1	
Esophagus	1	
Peritoneum		10
Ascites only	9	
Ascites and infiltration	1	
Kidneys		8
Pancreas		8
Pericardium		8
Effusion only	6	
Infiltration only	2	
Adrenal glands		7
Diaphragm		3
Uterus		2
Breast		2
Skin		2
Thyroid gland, trachea, aorta, ovary, bladder		1 each

* Multiple involvement.

The spleen has been described as the sole site of the disease. In our series other organs were always involved.

Histologically, the lesions in the spleen resemble those in the lymph nodes.

The liver is frequently affected. It was involved in 38 per cent of Sternberg's cases and in 55 per cent of our series. Massive enlargement of the liver is, in our experience, rare. The largest liver weighed 3500 gm. In 32 of the 63 autopsied cases the organ weighed more than 1800 gm., and in 18 of these foci of Hodgkin's

and some lymphocytes and plasma cells with little or no fibrosis In other cases the granulomatous infiltration shows a moderate or a marked degree of fibrosis in addition to the characteristic cytologic elements If there has been ulceration the picture is further complicated by superficial necrosis and the presence of numerous polymorphonuclear leukocytes

According to the literature (Siegmund Coronini) the intestinal granulomatous process is most frequently situated in the duodenum or the jejunum In our series there were lesions in the lower small intestine in 4 cases in the duodenum in 1 and the cecum in 1 The lesions appear as flat ulcers with raised rather firm edges and with irregular granular bases The bowel wall may be entirely encircled The granulomatous process also appears as plaques or tumorlike nodules that may obstruct the lumen and lead to intussusception Cases have been reported in which erosion of an artery at the base of a granulomatous ulcer has resulted in a fatal hemorrhage In 1 of our cases not included in the autopsy series because there was only an incomplete post mortem examination rupture of the small intestine resulted in the sudden death of a patient who had appeared the day before to be in excellent condition The possibility of such sudden deaths must always be borne in mind Microscopically the lesions resemble those found in the stomach

In 9 of our autopsied cases there was marked ascites in only 1 were there actual lesions of the peritoneum In all cases having ascites there was involvement of the retroperitoneal nodes

Involvement of the kidneys when the granulomatous process is widespread is not unusual In our series it occurred in 13 per cent of the cases There are usually small circumscribed nodules situated especially in the cortex We agree with Sternberg that massive lesions are distinctively rare The histologic picture needs no comment The ureters may be affected by extension of the process from neighboring lymph nodes

Secondary involvement of the pancreas by extension of granulomatous lesions of the stomach small intestine or retroperitoneal nodes is not very uncommon it occurred in 8 of our cases Primary involvement was not found although it has been described in the literature (Gruber)

The heart muscle was not invaded in any case but in 2 cases there were small nodules on the parietal pericardium Terplan and Mittelbach report such lesions as being frequent In 6 other cases in our series there was a moderate (100 to 300 cc) serous effusion

Eleven per cent of our cases showed involvement of the adrenal glands In each case there had been extension of the granulomatous process from adjacent lymph nodes Sternberg s experience was similar

The uterus was involved microscopically in 2 of our cases

Implication of the ovaries is rare In 1 of our cases there was a microscopic lesion

Sternberg (1936) reports 2 cases of Hodgkin s granuloma of the thyroid gland In 1 of our cases there were metastatic lesions in this organ

In none of our cases was the prostate gland involved Sternberg mentions 1 case reported in the literature No involvement of the testis or epididymis was

Such a condition may easily be mistaken, both by x ray and grossly at autopsy, for bronchiogenic carcinoma In the second type, grayish streaks of diseased tissue follow the course of the bronchi and usually represent an extension from affected mediastinal and tracheobronchial lymph nodes Invasion of the walls of the bronchi with compression or even occlusion of their lumens may occur In the third and rarest type, there are small to medium sized circumscribed nodules scattered diffusely through the parenchyma

Histologically, the process shows wide variations The granulomatous tissue may fill the alveoli without destroying their walls, on the other hand, the normal structures may be entirely destroyed and replaced by the granuloma In some cases very little connective tissue is present, the alveoli, however, containing numerous Reed-Sternberg cells Such a cellular type of lesion may be confused with Hodgkin's sarcoma, but in the lymph nodes and other organs from the same case the usual typical granulomatous process is present and therefore diagnosis is not difficult In other cases fibrosis is such an outstanding feature that the lesion resembles an organized pneumonia and careful search is necessary to detect Reed-Sternberg cells lying in the interstices of the dense connective tissue All variations between the distinctly cellular type of process and the highly fibrotic are encountered Cavity formation is rare and probably represents when it does occur a pyogenic infection of the granulomatous tissue, although in some cases if a bronchus has been occluded it is of the nature of a bronchiectatic abscess The formation of lesions beneath the visceral pleura is not uncommon The pleura is reported by Sternberg (1936) as being occasionally involved In 5 of our autopsied cases there was infiltration of the pleura without effusion in 3 there was serous effusion only, and in 2 there was serous effusion together with infiltration of the pleura In no case was the effusion bloody In every case in which there was effusion the mediastinal nodes were involved

Hodgkin's granuloma in the gastrointestinal tract may be either primary or secondary The secondary type is usually the result of the invasion from adjacent diseased lymph nodes or other organs In addition, secondary lesions appear as nodules in the serosa or mucosa, as the result of metastasis from a generalized granulomatous process

In our series of autopsies there were 6 cases of Hodgkin's granuloma primary in the gastrointestinal tract Three were primary in the stomach 1 in the ileum, 1 in the duodenum and 1 in the cecum These figures are in essential agreement with those of Sternberg

Grossly, the gastric lesion may appear as a polypoid tumorlike mass projecting into the lumen or as a broad based ulcer with firm raised edges It may lead to thickening of practically the entire wall with marked accentuation of the normal rugae This probably gives rise to the so called *Gehirnaspekt* in x ray films of the stomach considered by some as diagnostic of the disease There is usually extension to neighboring lymph nodes In rare cases only the local gastric lymph nodes are involved and no other organs or tissues show evidence of the granulomatous process

Microscopically the lesions in the stomach vary considerably In some cases the process is composed of numerous Reed-Sternberg cells many eosinophils

adenopathy extended from the level of the pancreas into the true pelvis

Of the remaining 9 cases, the disease was primary in the stomach in 3, in the tonsil in 2, and in the lung mediastinum para aortic nodes and brain in 1 each The lymph nodes were involved to a varying degree in all but one case, and peripheral lymphadenopathy was not uncommon (Table 7)

As might be expected the retroperitoneal tumors resulted in many complications, such as hydronephrosis, obstruction of the common bile duct, and venous

TABLE 7 *Lymph Nodes Found at Autopsy to Be Involved in 32 Cases of Hodgkin's Sarcoma*

TYPE OF NODE	NO OF CASES
Retroperitoneal	26
Mediastinal	14
Mesenteric	12
Axillary	11
Cervical	10
Inguinal	9
Para aortic	4

thrombosis due to compression by or invasion from adjacent tumor The tendency to invade neighboring structures, such as the pancreas, adrenal glands, and muscle was marked

The involved nodes were enlarged, often greatly so In some cases their outlines could be recognized in others the tumor had invaded the capsule, resulting in a large irregular shaped conglomerate mass In consistence the tumor may be fairly firm or soft or even practically diffluent As a rule however, the tissue cuts with ease and the cut surface is grayish white to white Areas of necrosis are not infrequent and appear as yellowish foci that may be extremely small or very extensive

Histologically the tumor is composed of cells two or three times the size of a normal lymphocyte The nucleus is usually round but may be ovoid The majority of the cells have single spherical nuclei with prominent nucleoli, but Reed-Sternberg cells with multilobed nuclei are always seen Their presence is necessary to establish the diagnosis of Hodgkin's sarcoma These cells vary considerably in number from case to case being numerous in some and few and far between in others It is our belief that the cells with a single spherical nucleus are undifferentiated forms of the Reed-Sternberg cell This theory is sustained by the staining reactions the character of the chromatin and the presence of transitional forms The cytoplasm of the tumor cells tends to stain neutrophilic or basophilic When stained with Mallory's phloxine methylene blue after Zenker fixation, the cytoplasm often has a granular or reticulated appearance Mitotic figures are usually numerous as would be expected in a highly malignant tumor

Apart from the tumor cells there are usually only scattered lymphocytes and reticulum cells The former are readily identifiable by their comparatively small size and the characteristically dense masses of chromatin Reticulum cells are easily recognizable by their finely divided scattered chromatin and acidophilic cytoplasm Neutrophils eosinophils, and plasma cells are rarely found unless the

found although a rare case has been described in the literature (Terplan and Mittelbach)

Sternberg found granuloma of the tonsil in 5 of his 52 cases The tonsils were enlarged and ulcerated In none of our cases were the tonsils involved

Rarely is there invasion of the diaphragm breast skin and certain other organs (Table 5)

Lesions of the central nervous system proper do not occur However com pression of the cord due to extradural masses or periosteal infiltrations of the vertebras is not infrequent In our series no case showed such lesions at autopsy Clinical evidence of meningeal involvement is however not uncommon It should be mentioned that patients with Hodgkin s granuloma may show signs and symptoms indicating cerebral involvement yet at autopsy no demonstrable ana tomic change can be found During life one of our patients (F S) had extraordi nary disturbances of taste and complete anorexia yet extremely prolonged and careful examination of the nervous system at autopsy failed to reveal even a microscopic lesion

Hodgkin s Sarcoma

Studies of 32 autopsied cases show that Hodgkin s sarcoma usually has its origin in the retroperitoneal lymph nodes and that the lesion is characteristically in vasive and destructive

The disease was primary in the retroperitoneal nodes in 23 (72 per cent) of our cases (Table 6) and in all cases the involvement was extensive and ex tremely destructive In 1 case there was a retroperitoneal mass of confluent lymph nodes weighing in the aggregate 1600 gm and direct extension from these nodes to the second and third parts of the duodenum the stomach the head of the pancreas and the lower surface of the liver In addition there was compres sion of the common bile duct and the aorta was buried in and partially com pressed by a mass of firm elastic nodes extending from the diaphragm to the bifurcation of the iliac vessels In another case a mass of lymph nodes extended along the entire length of the abdominal aorta and the tumor infiltrated the right psoas and the right latissimus dorsi muscles filled the entire right abdominal gutter and extended from deep within the pelvis to the twelfth right rib which was compressed and eroded by the tumor In a third patient the lymph

Table 6 *Apparent Pr mary S te of Disease in Cases of Hodgkin s Sarcoma*

	No of cases
Retroperitoneal lymph nodes	23
Stomach	3
Tonsils	2
Mediastinal lymph nodes	1
Para aortic lymph nodes	1
Lung	1
Cerebrum	1
Total	32

TABLE 8 *Organs Found at Autopsy to Be Involved in 32 Cases of Hodgkin's Sarcoma*

ORGAN		NO. OF CASES
Lymph nodes		31
Liver		19
Gastrointestinal tract *		15
Stomach	8	
Small intestine	4	
Duodenum	4	
Colon	4	
Esophagus	1	
Pancreas		11
Bones *		10
Vertebras	7	
Skull	3	
Pelvis	2	
Ribs	1	
Femur	1	
Lungs		10
Adrenal glands		9
Spleen		9
Kidneys		8
Muscles		5
Central nervous system		5
Pituitary gland	3	
Cerebellum	1	
Cerebrum	1	
Pericardium		4
Gall bladder		3
Thyroid gland		2
Tonsil		2
Testicle		2
Ovary, uterus, iliac vein, bladder and dura		1 each

* Multiple involvement.

stomach wall was invaded by primary tumor of the retroperitoneal nodes In the other two cases the tumor produced no visible macroscopic change

There were no tumors primary in the small or large intestine The small intestine or duodenum however was secondarily involved in 8 cases chiefly by metastasis The lesions appeared as grayish white nodules of varying size and number and were situated in the mucosa In 2 cases the large intestine showed metastatic nodules in the mucosa and in 2 cases it was invaded by extension of a primary tumor of the retroperitoneal lymph nodes In 1 case there was a microscopic lesion of the esophagus

It should be particularly noted that involvement of the gastrointestinal tract was not infrequently multiple and often extensive

The pancreas was affected by tumor in 11 cases (34 per cent) In 1 the tumor was apparently metastatic from a primary lesion of the tonsil The other cases represented direct extension from primary tumors of neighboring structures – the stomach in 3 cases and the retroperitoneal lymph nodes in 7

The bones were examined in 23 cases Ten of these showed tumor In 7 cases the vertebras were involved the tumor appearing as grayish nodules surrounded by red uninvolved marrow In 3 cases the skull had been invaded twice by

tumor is located in a region exposed to complicating inflammatory infiltration Areas of necrosis, usually of the infarct type, are not infrequent It should be emphasized that the diagnosis of Hodgkin's sarcoma rests, in the last analysis, on the presence of Reed-Sternberg cells

With silver stains, the reticulum fibers are usually found to be increased in number They enclose groups of cells as well as single cells In some cases the fibers are not only more numerous but also somewhat thickened

The structure of the affected node is destroyed by the diffuse growth of the tumor cells The capsule may be intact or may be extensively invaded, with extension of the neoplasm into the surrounding tissues

Aside from the lymph nodes, the organs most frequently involved in our series were the liver, the gastrointestinal tract, the pancreas, the bones, and the lungs (Table 8). The liver was involved to a greater or less degree in 19 cases (60 per cent) In 10 of these, the tumor occurred as grayish white nodules scattered throughout the parenchyma The size of such nodules varied widely from case to case but in each case they were of approximately the same size The smallest foci averaged 2 mm in diameter and the largest measured several centimeters In some cases only two or three tumor nodules could be found, whereas in others the organ was studded with them In 3 cases, the tumor was situated only in the capsule In 3 cases, there was direct extension into the liver, either from the stomach or from the retroperitoneal nodes

On the whole the liver was somewhat enlarged, the largest weighing 2900 gm, but the majority weighed approximately 2000 gm, and it is notable that in a number of cases the liver, although definitely involved, was no larger than normal, the few metastatic nodules being buried deep within its substance

Various portions of the gastrointestinal tract were involved in 15 cases (47 per cent) This is in sharp contrast to the comparatively uncommon involvement of the gastrointestinal tract in Hodgkin's granuloma In 3 cases, the disease was primary in the stomach In one of these, the tumor involved the posterior wall in its middle third, extending from the greater to the lesser curvature and causing an ulceration over an area measuring 12 by 4 cm There was considerable erosion at the base of the ulcer, and extensive hemorrhage had taken place from it The tumor was white and necrotic and cut easily In another case, the tumor appeared as a craterlike ulcer, 4 cm in diameter, situated 2 cm above the pylorus The edges of this area were elevated 0 3 to 0 4 cm above the surrounding mucosa and were made up of moderately firm, white tissue The center of the crater was soft and homogeneous On section, the tumor was found to extend into the pancreas and between the vertebral bodies In the third case, the tumor occurred at the cardiac end of the stomach and involved an area 14 cm in diameter From the mucosal aspect, the neoplasm appeared as a plateaulike elevation one portion of which was cauliflowerlike, and measured 4 cm in diameter, the surface was ulcerated and greenish gray. The tumor tissue was homogeneous, pinkish gray, and soft

In 5 other cases, the stomach was secondarily involved In one, the tumor appeared as an ulcer, in another, as raised patches in the mucosa In a third the

nervous system proper has been reported In 1 case the tumor was primary in the paravertebral lymph nodes and had extended between the transverse process of the vertebras from the third cervical to the eleventh dorsal invading the dura and causing marked compression of the spinal cord in the upper cervical region. In another there was a metastasis from a primary tumor of the retroperitoneal lymph nodes to the cerebellum This was described as a ridge of tumor measuring 5 by 3 by 0 5 cm and extending along the superior surface of the cerebellum Microscopic examination revealed extensive invasion of the cerebellum well into the dentate nucleus In one case the frontal lobe was involved by a primary tumor

The pituitary gland was involved in 3 cases In 1 case in which the tumor was primary in the tonsil the gland was invaded and its normal structure obliterated In another it was surrounded and compressed by neoplastic tissue but was not actually invaded In the third microscopic examination revealed invasion of the capsule and the peripheral portion of the pars nervosa the tumor was primary in the retroperitoneal lymph nodes

In 3 cases there was a moderate serous effusion into the pericardial sac and in another a small nodule of tumor was seen in the parietal pericardium itself

In 3 cases there were small metastatic nodules in the gall bladder

In 2 cases the thyroid gland was implicated each time by a metastasis secondary to tumor primary in the retroperitoneal nodes In 2 cases metastatic nodules were found in the testes

There was involvement by the tumor of the following organs in 1 case each ovary uterus iliac vein bladder and dura

Summary

Hodgkin s paragranuloma characterized by the presence of Reed-Sternberg cells in the absence of necrosis or fibrosis appears to be a disease essentially of lymph nodes With the passage of time it may become transformed into the more malignant Hodgkin s granuloma

Hodgkin s granuloma characterized by the presence of Reed-Sternberg cells pleomorphism eosinophils necrosis and fibrosis, may involve any organ of the body with the exception of the central nervous system proper and is frequently widespread

Hodgkin s sarcoma characterized by the presence of typical Reed-Sternberg cells scattered among cells that are probably extremely anaplastic forms of Reed-Sternberg cells behaves as a true tumor is highly invasive and malignant and may involve any organ of the body including the central nervous system proper

Transitional forms of these three types of Hodgkin s disease occur but it is essential for the understanding of the clinical features to recognize the existence of each.

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d rect extension from tumors primary in the tonsil In the first of these there was a pedunculated growth on the superior part of the occipital bone The region of the sella was markedly widened and the pituitary was involved by soft grayish tissue The bony structures surrounding the fossa were softened The tumor also occupied the entire sphenoidal sinus had eroded the surround ing sphenoidal structures and was found as well in the foramen lacrum of the petrous portion of the temporal bone In the second case the tumor invaded and partly destroyed the antrum and bones of the orbit on one side In the third case involvement of the skull was apparently metastatic from the retroperitoneal lymph nodes In the region of the right temple there was a superficial swelling of the scalp 8 cm in diameter The inner table of the skull beneath this was shaggy and the entire thickness of the bone was involved by tumor that had extended through to the dura which was diffusely invaded There was however, no extension to the pia arachnoid

There was 1 case of involvement of the great trochanter of the femur In 2 cases the tumor primary in the retroperitoneal nodes had extended directly to the pelvic bones In another case the ribs showed multiple tumors secondary to a primary lesion of the para aortic lymph nodes

Ten cases showed involvement of the lungs at autopsy In 1 the tumor was primary in the right lower lobe and owing to the extensive involvement and the apparently abrupt onset the case on admission was mistaken for one of lobar pneumonia At autopsy the grayish white tumor occupied practically the whole of the lower lobe and was necrotic in its center In 2 cases there were scattered nodules approximately 1 cm in diameter Two cases grossly showed no visible tumor but it was present microscopically In the other 5 cases the tumor had extended in from the mediastinal nodes along the bronchi

The adrenal glands were involved in 9 cases in each by direct extension from tumors arising in adjacent lymph nodes

The spleen was involved in 9 cases much less often — and far less extensively — than in Hodgkin s granuloma In 1 case there was direct extension from a tumor primary in the retroperitoneal lymph nodes in the form of a yellow white mass extending in from the hilus in a radial manner for some 6 cm The splenic artery and vein were surrounded by the neoplasm but were not invaded by it In 2 cases the spleen showed only microscopic lesions In the remaining cases there were one or more grayish white nodules varying in diameter from 0 1 to 1 0 cm The involved spleens were uniformly but not greatly enlarged the heaviest of them weighing 640 gm

The kidneys were involved in 8 cases in each of which the tumors were metastatic In no case did they result from invasion from surrounding structures In every case each kidney was involved to a similar degree The tumor nodules were less than 1 cm in diameter and were usually situated in the cortical region

There was invasion by tumor of the muscles of the thoracic wall in 1 case of the psoas muscle in 3 of the quadriceps in 1 and of the diaphragm in 1

The central nervous system was involved in 16 per cent of the autopsies Again one sees the sharp contrast between Hodgkin s sarcoma and Hodgkin s granuloma in which so far as we are aware no involvement of the central

nervous system proper has been reported In 1 case, the tumor was primary in the paravertebral lymph nodes and had extended between the transverse process of the vertebras from the third cervical to the eleventh dorsal, invading the dura and causing marked compression of the spinal cord in the upper cervical region In another, there was a metastasis from a primary tumor of the retroperitoneal lymph nodes to the cerebellum This was described as a ridge of tumor measuring 5 by 3 by 0 5 cm and extending along the superior surface of the cerebellum Microscopic examination revealed extensive invasion of the cerebellum well into the dentate nucleus In one case the frontal lobe was involved by a primary tumor

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TABLE 1 *Initial Symptoms of Hodgkin's Paragranuloma* (28 *Cases*)

SYMPTOMS	NO OF CASES
Painless nodes in neck	23
Painless nodes in groin	2
Painless nodes in axilla	1
No symptoms	2

elapse before the development of Hodgkin's granuloma, in still others, the condition remains quiescent for many years, and death may be due to some intercurrent disease, or the patient may survive and remain in excellent health for many years In these last cases, however, there is always the possibility that the disease will once more become active or that Hodgkin's granuloma will develop This has been seen to happen as long as nineteen years after the initial lesion was discovered Involvement of the mediastinal lymph nodes may take place this does not necessarily imply that Hodgkin's granuloma is developing, but enlargement of the spleen has, in our experience, been an ominous sign The onset of systemic symptoms, such as fever, weakness, anorexia or loss of weight, almost always indicates that a transition to the granulomatous form has taken place There is no characteristic blood picture, although one occasionally finds an increased percentage of polymorphonuclear neutrophils There is no anemia

The following case histories illustrate the course of the disease

CASE 1. J H (Pv 5-42), a 40 year-old man, was first seen on 20 May 1942 Six

was normal A moderate amount of x-ray therapy was given to the left groin and to the node in the axilla

The patient remained well until September 1942, when he noticed *some pain* in the right upper quadrant of the abdomen and increasing weakness necessitating his resting when he returned home from work At *that time, there were* a few small lymph nodes in both sides of the neck and in each groin The spleen

Otherwise the physical examination

cell count was normal but the white-

cent polymorphonuclear neutrophils

A moderate amount of x ray therapy was given to each quadrant of the abdomen, and the patient improved considerably and gained weight Nevertheless a month later he again began to feel poorly and noted an elevation of temperature each afternoon He was readmitted to the hospital and was found to have generalized lymphadenopathy The red cell count had fallen to 3,900 000 and he was therefore given several transfusions of whole blood The x ray examination of the chest showed numerous small patches of consolidation the nature of which was somewhat uncertain although it was believed that since *several of them* were definitely nodular, the lesions probably represented metastases from a newly developed Hodgkin's granuloma This suspicion seemed to be substantiated by

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3 SYMPTOMS AND COURSE

In the present section the initial symptoms of the three types of Hodgkin's disease will be discussed, and the general course of the disease will be briefly illustrated In a subsequent section, the symptoms and signs arising from involvement of certain organs will be discussed in more detail

Hodgkin's Paragranuloma

Hodgkin's paragranuloma is a comparatively benign condition, the onset of which is virtually always heralded solely by painless lymphadenopathy, usually in the cervical region (Table 1)

Systemic symptoms are absent at first, and the patient appears to be in good health Occasionally the disease is discovered on routine physical examination

According to our experience, approximately 20 per cent of the cases progress after months or years to Hodgkin's granuloma It must be emphasized that the insidiousness of the onset in no way precludes this development and, as we have already pointed out those cases that progress cannot, even by the most careful histologic study, be distinguished in their incipiency from those that do not

The course of Hodgkin's paragranuloma is extremely variable In certain cases, there develop signs or symptoms suggesting a transition to Hodgkin's granuloma, and death ensues within a short time, in others, many months or several years

tion, any lesion, either gross or microscopic, in the nervous system to account for the hemianopsia or the abnormality of taste A few enlarged lymph nodes, particularly about the head of the pancreas and in the retroperitoneal area, showed the histologic changes of Hodgkin's granuloma The most prominent lesion seen was an extreme degree of amyloidosis chiefly in the lymph nodes, kidneys, liver, and spleen Although Hodgkin's granuloma was found at autopsy, the lesions were not extensive enough to cause death which must be attributed to inanition following extreme anorexia, the cause of which remains entirely obscure

CASE 3 J H (B C H 408240), a 17 year old man was admitted to the hospital on 22 September 1920, with the sole complaint of painless lymph nodes in the right side of the neck The past history had been uneventful In 1915 he noted a few small lymph nodes in the right side of the neck These increased slowly in size and in 1917 one was removed for diagnosis. No record of this biopsy had been preserved In August 1920, the patient complained of an increasing sense of constriction in the neck and upper thorax and noticed that the lymph nodes in the cervical region had increased greatly in size

Physical examination at that time revealed no abnormalities except for the presence of a large number of firm, elastic nodes in the right side of the neck, extending from the mastoid region to the supraclavicular area A radical dissection was done and all the apparently diseased tissue was removed Examination of the lymph nodes showed the typical picture of what we now recognize as Hodgkin's paragranuloma Unfortunately the patient was told by one of his friends that he would die in six months, and as a respite from this gloomy outlook, he had recourse to hard liquor in large amounts At the end of a year he was still alive but was unable to forego alcohol He remained symptom free, however until September 1939 when he again noticed nodes above the clavicle and a sense of tightness in the neck Physical examination showed many firm nodes above the right clavicle these appeared to extend into the thoracic cage A biopsy showed that the process had progressed into a typical Hodgkin's granuloma A large mediastinal mass developed and in spite of x ray therapy the patient died in 1942 twenty seven years after the initial lymphadenopathy and three years after the known transition of the Hodgkin's paragranuloma into Hodgkin's granuloma

CASE 4 L C (Pv 2–36), a 36 year-old woman was admitted to the hospital in April 1936 In 1910 at the age of 10 years enlarged lymph nodes had appeared in the right side of the neck These had been removed at another hospital and showed the histologic picture of what we now call Hodgkin's paragranuloma The patient remained entirely well until 1917, when the nodes recurred They were removed and again showed precisely the same features as they had in 1910

No further signs or symptoms occurred until February 1936 when masses were once more noted in the right side of the neck Physical examination showed no abnormalities except that beneath the upper third of the right sternomastoid muscle were a group of firm freely movable nodes These were excised as completely as possible and they too showed the histologic features of Hodgkin's paragranuloma Thus there had been no appreciable change in the histologic picture since 1910 Thirty five years after the initial lymphadenopathy the patient is free of signs and symptoms

the fact that the pulmonary lesions cleared up after an x ray dosage of 1600 r had been given to the chest X ray therapy was then directed to the peripheral lymph nodes The patient's general condition, however, did not improve The fever continued, and he began to have drenching night sweats

In January 1943, generalized lymphadenopathy appeared The red cell count gradually fell to 1,600 000 and the hemoglobin to 35 per cent Following further x ray therapy and several blood transfusions, the patient improved somewhat and the fever subsided After a very short time, however, the weakness and fever returned and the patient grew steadily worse until his death on 20 March 1943

Autopsy showed widespread involvement by typical Hodgkin's granuloma

This case illustrates the rapidity with which Hodgkin's paragranuloma occasionally develops into Hodgkin's granuloma

CASE 2 F S (Pv 8-29), a 45 year old man, in 1927 first noticed a few small, painless lymph nodes beneath the right sternomastoid muscle In 1929 a node was removed that on subsequent review showed the typical picture of Hodgkin s paragranuloma There were no general symptoms at that time, the patient felt perfectly well and no other abnormalities were noted on physical examination X ray treatment was given to the right cervical area, and the patient remained entirely asymptomatic for 6 years — until March 1935 — when enlarged lymph nodes were noted in the left side of the neck These were excised and showed a histologic picture suggesting a transition between Hodgkin's paragranuloma and Hodgkin's granuloma X ray therapy was again given, the lymph nodes subsided, and the patient remained asymptomatic until March 1938 At that time he developed a moderate degree of anorexia and definite bitemporal hemi anopsia He became weak, listless, and apathetic Physical examination was essentially normal except that the visual fields were notably contracted and the spleen could be felt 3 cm below the costal margin He was given an x ray dosage of 600 r at 250 kv to each side of the head, and his symptoms entirely subsided

In June 1938 the anorexia returned In addition, the patient, a highly intelli gent man of robust stature, noticed that all food tasted unusually sweet With the passage of time this sense of sweetness became so great that the patient, al though co operative, was unable to eat anything except the most highly spiced foods, and but little of these A large mediastinal mass was visualized by x ray, and a moderate degree of hypochromic anemia had developed The white cell count, normal at all previous examinations had risen to 17,000, with 85 per cent polymorphonuclear neutrophils The patient was given an x ray dosage of 1000 r at 250 kv to the head with some temporary relief from the sensation of sweetness The mediastinal mass completely disappeared after 800 r to the anterior part of the chest The anorexia, however, became increasingly severe, and for the next six months the patient subsisted almost entirely on peptonized milk and hard boiled eggs, to each of which he added in order that they might not taste too sweet,' astounding amounts of cayenne pepper There was no suggestion of hysteria, and all those who examined him were convinced that the symptoms had an organic basis, although no one was able to localize the lesion He be came extremely emaciated, as might well be expected, and died on 27 April 1939, ten years after the onset of his condition

Autopsy failed to reveal, even after the most careful and scrupulous examina

tirely There were no constitutional symptoms In January 1938 the patient developed an acute upper respiratory infection of considerable severity and immediately thereafter the cervical nodes increased rapidly in size

On entry to the hospital physical examination revealed an obese healthy looking woman In the anterior and posterior triangles of the left side of the neck and beneath the sternomastoid muscle were several firm nontender lymph nodes varying from 2 to 5 cm in diameter There was no other lymphadenopathy but the upper part of the mediastinal shadow was definitely widened in the x ray film Aside from a moderate elevation of the white cell count and an increase of the percentage of polymorphonuclear neutrophils in the peripheral blood the laboratory findings were within normal limits A biopsy of one of the cervical lymph nodes showed Hodgkin s granuloma Appropriate x ray therapy was directed to the neck and mediastinum with complete disappearance of all masses The patient was still in excellent condition and gaining weight when last seen in May 1944

In an adult the persistence of notably enlarged lymph nodes for a considerable period of time after an acute upper respiratory infection or the development of persistent masses in the neck after minor infections must be regarded with suspicion particularly if the posterior triangle or the supraclavicular region is involved Painless enlargement of lymph nodes in the neck unassociated with obvious infection always calls for careful investigation and it has been our experience that without biopsy an accurate and definitive diagnosis cannot be made

The enlarged lymph nodes are usually nontender and rarely cause pain unless they press on adjacent nerves or are adjacent to obvious septic foci Later pain due to lymphadenopathy is more frequent particularly when the lymph nodes are in the groin or the axilla The overlying skin is usually normal in appearance *and the nodes are seldom fixed to the surrounding structures although they* may become immobile by the very fact that they fill the entire neck and impinge on contiguous fixed structures It should be borne in mind however that as a result of poulticing or other self med cation the overlying skin may become reddened and that an associated infection in the nasopharynx may cause the nodes to be temporarily painful and tender even in the early stages of the disease In consistence the nodes are usually firm and rubbery occasionally soft, and rarely hard They never have the stony feel so suggestive of metastatic carcinoma unless they have already been subjected to heavy radiation On rare occasions the nodes are extremely soft

In our experience there is no predilection for one or another side of the neck and in the majority of cases the involvement is bilateral when the patient is first seen although almost invariably one side is involved to a far greater extent than the other and only rarely does one see the evenly distributed bilateral nodes of uniform size and relatively soft consistence so often found in lymphatic leukemia No particular part of the cervical region appears to be most frequently involved It is wise however to search with special care for nodes beneath the sternomastoid muscles and in the region immediately above the clavicles Enlarged nodes are not infrequently found in the submaxillary and submental regions but those confined sharply to such regions are rarely due to Hodgkin s

granuloma and are likelier to be secondary to some obscure infection of the floor of the mouth This fact may be of some practical value in diagnosis

Enlarged lymph nodes elsewhere, as in the axilla and inguinal regions have in general the same characteristics as those in the neck, although they are more prone to be painful and only rarely fluctuate in size, probably owing to the fact that they are less likely to be influenced by adjacent infectious processes

Pain is the next most frequent initial complaint, but it should be emphasized that early in the course of Hodgkin's granuloma this symptom is comparatively rare In Hodgkin's sarcoma and reticulum cell sarcoma, on the other hand, pain is often an early, and almost constantly a late, symptom The most frequent sites of pain are the abdomen and the back In the former, it is in most cases caused by retroperitoneal lymph nodes, and it is perhaps surprising that this symptom is not found oftener, for many authors have emphasized the frequency with which the retroperitoneal nodes are involved, and our own experience is in agreement with this finding

Only rarely is pain due to invasion of one of the abdominal viscera, as in the following case

CASE 6 E M (B C H 559573), a 47 year old man, was admitted to the hospital on 10 May 1923 with a chief complaint of upper abdominal pain Thirteen years previously he had been operated on for a 'perforated gastric ulcer' No data were available as to the nature of this ulcer Convalescence, however, had been uneventful, and the patient remained symptom free until January 1923, at which time he began to suffer from a burning epigastric pain occurring shortly after meals and lasting approximately an hour There was no nausea or vomiting During the next three months, he lost about 15 pounds and three days before entry to the hospital he vomited 'a cupful' of bright red blood

Physical examination on admission showed evidence of an old healed tuberculous process in the apex of the right lung and a moderate degree of anemia The abdomen showed no tenderness, spasm, or masses X ray examination revealed an extensive irregularity and mottling of the cardia and media of the stomach, and a diagnosis of carcinoma was made The red cell count was 3 280,000, the hemoglobin 55 per cent, the white cell count was 16,000, with 86 per cent polymorphonuclear neutrophils 10 per cent lymphocytes, and 4 per cent monocytes The stools gave a strongly positive guaiac test The patient failed rapidly and in spite of two blood transfusions, the red cell count fell to 2 800 000 and the hemoglobin to 40 per cent Persistent vomiting developed, and he died three weeks after entry

Autopsy showed extensive Hodgkin's granuloma of the stomach with extension into the liver and pancreas and involvement of the gastric and retroperitoneal lymph nodes

Rarely abdominal pain is caused by great enlargement of the spleen

Pain in the back usually in the lower thoracic or lumbar region, may be due to a variety of causes In obscure cases, one is often forced to the conclusion that enlarged lymph nodes are pressing on one or more spinal nerves Not infrequently back pain is due to direct involvement of the bodies of the vertebras or to granulomatous lesions in the dura or epidural space, and it is of the greatest importance to recognize the fact that lesions of the spine may be present for

several months before they can be visualized on x ray films Pain due to involvement of bone is well illustrated by the following case

CASE 7 B B (H H 36-543), a 34 year-old woman, was admitted to the hospital on 25 May 1936 In February 1933, she began to complain of fleeting pains of no great severity in the low lumbar region The pain was made worse by exercise, and was not constant A careful physical examination at that time by her physician revealed only slight tenderness and spasm of the muscles in the right lumbosacral region The symptoms continued with exacerbations and remissions, in spite of baking, massage, and simple orthopedic measures, until May 1935 The pain then became constant, was much worse at night and radiated from the lumbar region bilaterally to the lower abdomen Nine months later, in February 1936, the patient began to lose weight and to complain of anorexia, nausea, and occasional attacks of vomiting

Except for evident loss of weight – she had lost 29 pounds – the physical examination showed only a few discrete, firm, bean sized lymph nodes in each side of the neck The red-cell count was 3 890 000, the hemoglobin 63 per cent, and the white-cell count 33 000, with 90 per cent polymorphonuclear neutrophils and 10 per cent lymphocytes X ray films of the spine and pelvis showed extensive hyperplastic changes in the bodies of the third, fourth and fifth lumbar vertebras and in the left portion of the pelvis consistent with those of Hodgkin's granuloma A biopsy of a small node in the right side of the neck showed the typical picture of that condition X ray therapy relieved the back pain for a few months, but splenomegaly, hepatomegaly, and a left sided pleural effusion developed, and the patient died in early October 1937, nineteen months after the bone lesion had been demonstrated by x ray

When the Hodgkin's granuloma actually first developed is, of course, problematical, but this case illustrates the importance of careful x ray studies in patients with obscure and recalcitrant back pain, and the wisdom of searching for enlarged lymph nodes that may give a clue as to the true condition

Pain in the chest, shoulder, groin, leg, or axilla is occasionally encountered as an initial symptom Usually under such circumstances unequivocal evidence of Hodgkin's granuloma is present

Generalized weakness is not infrequently the first symptom and in the absence of obvious lymphadenopathy or splenomegaly, may be a most difficult one to evaluate A careful search should be made for enlarged lymph nodes and abdominal masses, and the finding of an elevated basal metabolic rate or an elevated white cell count with an increased percentage of polymorphonuclear neutrophils may be of some diagnostic significance

Not infrequently, symptoms referable to the gastrointestinal tract first attract the patient's attention If there has been melena or hematemesis some intrinsic lesion is usually discovered at autopsy Other symptoms, such as anorexia and nausea, can only rarely be traced to such an intrinsic lesion

Finally, there are a considerable number of the most varied initial signs and symptoms, such as anorexia, edema of the legs, dyspnea, loss of weight abdominal masses, cough generalized itching amenorrhea, hemoptysis, persistent sore throat, vomiting, hematemesis, dysphagia, melena, and deafness One can

only bear in mind that Hodgkin's granuloma may first manifest itself in such ways and endeavor to prove whether it is present

In a considerable number of cases there is initially a combination of several symptoms, in which event the condition is usually already well advanced Yet it should be pointed out that this fact by no means necessarily militates against relatively successful therapy

It is thus clear that Hodgkin's granuloma is usually first manifest by painless cervical lymphadenopathy, but that its initial stage may be marked by the most diverse symptoms and signs

GENERAL COURSE

In the great majority of cases, Hodgkin's granuloma progresses inexorably to a fatal termination, but the course is extremely variable and, aside from the broadest generalities it is impossible in any given case to predict what changes will take place or precisely when they will occur Virtually any organ or tissue in the body may be involved, and the clinical course of the disease depends in large measure on the extent and rapidity of the spread as well as on which organs are involved In one case, the pathologic changes may become so widespread and so all inclusive that no organ can properly fulfill its function, and death ensues from a sort of general attrition, in another, sudden death may occur at a time when the patient seems to be in comparatively good health

The disease does not advance in an even, orderly fashion Remissions occasionally occur in a quite unpredictable manner, and patients who have seemed to be failing under the best of treatment may unaccountably respond most favorably to what is regarded as a final therapeutic gesture On the other hand, it is not unusual to see a patient who has been doing especially well for many months or even years become rapidly worse and die within a few weeks

In view of these facts, it seems profitless to attempt any working classification of the various clinical types that are met with in practice It is true that in one case the process may be confined largely to the mediastinum, in another to the spleen, and in still another to the gastrointestinal tract In some cases anemia is a marked feature, in others, high fever A patient may be seen in whom loss of weight and strength has been, from the onset, a striking feature, again, a patient may be able to continue hard physical labor until the end is but a short way off In this sense, there are clinical types, yet each case is a law unto itself, and the disease can be treated more intelligently if this fact is constantly borne in mind

Hodgkin's granuloma only rarely progresses into Hodgkin's sarcoma, a far more malignant form of the disease Such transformation is far less frequent than the comparable progression of Hodgkin's paragranuloma into Hodgkin's granuloma

The following cases illustrate the varied course of Hodgkin's granuloma

Case 8 C C (C H 167400), a 6 year old girl, was admitted to the hospital on 1 January 1933 The past history was irrelevant She had always seemed healthy Approximately three weeks before entry, the parents had noticed enlarged lymph nodes in each side of her neck These increased rapidly in size,

and a week later she developed a severe cough associated with some hoarseness and a moderate elevation of temperature. For a week before entry, she had had marked anorexia.

Physical examination on admission revealed a well developed and well nourished girl suffering from a marked degree of dyspnea. In the posterior triangle of both sides of the neck were numerous rubbery lymph nodes 1 to 4 cm. in diameter. They were not attached to the skin or to the underlying tissues. The throat appeared normal. Examination otherwise revealed nothing abnormal except for a pronounced widening of the mediastinal dullness, a finding that was confirmed by x-ray examination. The temperature was 102°F., the pulse 140, and the respirations 30. The red cell count was 3,600,000 and the white cell count 13,400, with 72 per cent polymorphonuclear neutrophils, 2 per cent myelocytes, 20 per cent lymphocytes, and 6 per cent monocytes. A biopsy of one of the cervical lymph nodes showed the picture of Hodgkin's granuloma. The patient's dyspnea increased, the temperature rose to 104°F., and she died of respiratory failure less than a month from the apparent onset of her condition.

CASE 9. K.A.D. (H.H. 36-542), a 20-year-old man, was admitted to the hospital 25 May 1936. A year before entry, he had had a mild upper respiratory infection, following which there had appeared an enlarged lymph node in the right side of the neck. There was no impairment of general health. The node was neither tender nor painful, but it persisted after the subsidence of the respiratory infection. Eight months later the patient's family noticed that he was becoming pale. For several weeks before admission, he ran a septic type of temperature and had many drenching night sweats. Shortly thereafter, there appeared edema of the ankles and scrotum, and coincidentally both the hearing and vision began to fail.

Physical examination on entry showed an emaciated man lying apathetically in bed. His vision was markedly impaired; he could not read the largest newspaper type. The left eye showed a moderate degree of enophthalmos and was deviated downward and inward. The right fundus oculi showed several patches of exudate similar to that seen in chronic nephritis, and, in addition, a large area of chorioretinitis on the temporal side of the disk. In neither ear could the patient hear the tick of a watch. Both nostrils were filled with clotted blood, and the lips were parched, cracked, and bleeding. In the right side of the neck from the angle of the jaw to the supraclavicular space were many firm, discrete lymph nodes averaging 2 cm. in diameter. Recently there had been excised from this region a lymph node showing the typical picture of Hodgkin's granuloma. In each groin were large numbers of firm, tender lymph nodes, and many similar ones could be felt deep in the pelvis above the pelvic brim. The heart was normal in size. Signs of moderate ascites were present, but neither the liver nor the spleen could be felt. There was marked edema of both legs and of the scrotum and penis. The red-cell count was 2,130,000, the hemoglobin 30 per cent, and the white-cell count 2000, with a normal differential count. The platelets were greatly diminished. The urine contained a slight trace of albumin and a few red cells. The temperature was 103°F., and the pulse 130.

Since the disease was obviously widespread, involving the ears, eyes, chest, abdomen, pelvis, bone marr[illegible] dition seemed desperate, it [illegible] instituting x ray therapy. I[illegible]

Between 26 May and 11 June, three blood transfusions totaling 1600 cc were given, with the result that the hemoglobin rose to 50 per cent and the red cell count to 3,500 000 During the interval, his general condition remained essentially unaltered but, interestingly enough, the hearing improved sufficiently so that the patient could hear a watch tick in both ears and could understand normal conversation The eyesight also improved although not to the same extent The patient's condition appeared to warrant the institution of x ray therapy, and, inasmuch as the most marked lymph node involvement was in the pelvis radiation was directed to that area, and from 11 to 15 June he received 275 r of high voltage x rays He suffered no untoward reaction to this small amount of radiation, so that between 15 and 22 June he was given 1000 r to the abdomen The temperature remained elevated, the physical examination was essentially unaltered, and the general condition seemed, if anything rather worse The patient became jaundiced and even during the day was somewhat drowsy He took no notice of his surroundings, and it was difficult to arouse him from his almost constant lethargy The red cell count had fallen to 1,940,000 and the hemoglobin to 32 per cent

The outlook was certainly not bright and all therapeutic measures to date appeared to have been unavailing In view of the falling red cell count, the patient, between 1 and 10 July, was given transfusions totaling 3000 cc of blood, with a resultant rise of the red cell count to 3,480,000 By that time, the temperature had come down to normal, the hearing was normal, and the eyesight, although still poor, was much improved The patient was allowed up and around the wards within the limits of his strength His appetite, which on admission had been practically nil was now ravenous His general condition improved daily, and he rapidly gained both strength and weight The emaciated, apathetic boy first seen became an optimistic young man The lymph nodes in all areas became much smaller The ocular manifestations improved, with the exception of the retinal changes, which remained unaltered The peripheral edema and ascites disappeared On 20 July, the patient was given another blood transfusion of 500 cc, and on 25 July he walked out of the hospital to return to his home

In August of the same year, the cervical lymph nodes returned and increased rapidly in size but, after administration of 600 r to each side of the neck, they completely disappeared, and the patient seemed in excellent condition and was able once more to return to work as a laborer

He continued to work at hard manual labor until December 1936, when he again became weak and complained of anorexia nausea and vomiting, and ringing in the ears There were many firm lymph nodes in each side of the neck The mediastinal shadow was increased to the right, and the spleen was palpable 3 cm below the costal margin The temperature was 103°F, the pulse 130, and the respirations 35 Examination of the blood showed a red-cell count of 1 570,-000 and a white cell count of 4000 The patient was given three blood transfusions of 500 cc each and 75 r of spray x ray therapy, both anteriorly and posteriorly Following this his general condition improved greatly, the lymph nodes and spleen disappeared, and he was once more able to resume his normal activities In May 1937, however, he was again troubled with anorexia and vomiting and the temperature rose to 102°F The spleen was barely palpable on inspiration Many fine rales appeared at the apex of the right lung There was no return of the lymph node enlargement, but the patient failed steadily and again became partially blind and deaf The temperature remained constantly

between 101 and 103°F the red cell count fell to 2 630 000 and the patient died on 25 August 1937 which was two years and three months after the date of his first symptom

CASE 10 E M (P H 1887) a 52 year-old man was in excellent health until May 1929 when he noticed a small lump in the left axilla It was neither painful nor tender and he had no other complaints Physical examination showed a firm mass 6 cm in diameter high in the left axilla a pea sized lymph node above the left clavicle and a similar one in the left epitrochlear region Otherwise the examination showed no abnormalities The red cell and white cell counts were within normal limits and x ray films of the chest failed to show any widening of the mediastinal shadow The axillary and epitrochlear nodes were excised and each showed the typical histologic picture of Hodgkins granuloma The patient was given 900 r to the left axilla and 600 r to the left epitrochlear region

There have been no recurrences and the patient has remained well to date seventeen years from his first symptom

CASE 11 J P (P H 2757) a 48 year old Italian laborer noted in August 1930 ease of fatigue anorexia night sweats and a mass in the left axilla he continued at his work however Three months later there appeared an enlarged lymph node in the right axilla This was removed and showed the usual picture of Hodgkins granuloma He was admitted to the hospital on 6 December 1930

Physical examination revealed a firm nontender lymph node 4 cm in diameter in the left axilla and several similar ones in the left supraclavicular area The spleen was palpable 3 cm below the costal margin An x ray film of the chest was normal, and it was specifically noted that there was no evidence of bone involvement The general condition was good The red cell count was 3 850 000 the hemoglobin 60 per cent and the white cell count 11 400 with 79 per cent polymorphonuclear neutrophils 1 per cent eosinophils 15 per cent lymphocytes and 5 per cent monocytes Six hundred r was given to the left

Three weeks later how

in diameter over the

sive irregular mottling

and destruction of the gladiolus and on physical examination there was a hard tender swelling rising 2 cm above the general level of the sternum and 10 cm in diameter The patient was given 600 r to the left side of the neck each axilla and the spleen and 1000 r over the sternal mass The nodes disappeared following this treatment The sternal mass became much smaller but did not disappear

During the intervening years he has received 2400 r to the involved area The last x ray films still showed the bony destruction but when last seen in the spring of 1945 16 years after his first symptoms the patient was feeling perfectly well and was capable of doing reasonably hard manual labor

Cases 10 and 11 attest the value of early treatment and show that Hodgkins granuloma is not always so rapidly fatal as is generally believed

CASE 12 A P (H H 17-646) a 10 year old boy in 1915 noticed a plum sized mass in the right side of the neck This was excised and showed the histologic features of Hodgkins granuloma Physical examination revealed no other ab

normalities and both the past and family histories were noncontributory The peripheral blood picture was normal At intervals during the next 8 months 8200 m c h of radium was given at the site of the lesion and 800 m c h to the mediastinum

For the next 15 years the patient remained entirely well except that from time to time minute nodes were noted under the anterior part of the jaw This minor lymphadenopathy appeared to be due to oral sepsis

In 1930 at a routine checkup there was found a mass the size of a small plum in the submaxillary region on the left side This was removed and again showed the picture of Hodgkin s granuloma An indeterminate amount of x ray (probably about 600 r) was directed at the left side of the neck The patient thereafter remained free of all signs and symptoms up to December 1943 when he moved to another city and was lost sight of

Whether this result can properly be regarded as a cure in the true sense of the word is perhaps debatable That the results were excellent no one can deny for the patient was alive and well nearly thirty years after the initial lymphadenopathy

Hodgkin s Sarcoma

Pain is the most frequent initial symptom of Hodgkin s sarcoma (Table 3) It is most frequent in the abdomen is usually unrelated to meals and is occasionally accompanied even early in the disease by loss of weight Pain may of course occur elsewhere and it is to be particularly noted that the superficial lymph nodes are often painful This is rarely the case in Hodgkin s granuloma Painless lymphadenopathy may be the sole initial symptom but the enlarged lymph nodes seldom fluctuate in size as they frequently do in Hodgkin s granuloma Weakness dyspnea cough and vomiting may be seen early Rapid loss of weight is much more frequent than in Hodgkin s granuloma and may be the outstanding feature of the disease Thus pain was an initial complaint in over 50 per cent of our cases of Hodgkin s sarcoma whereas it was present initially in only 12 per cent of patients suffering from Hodgkin s granuloma Symptoms suggesting involvement of internal organs were noted at onset in 75 per cent whereas

Table 3 *Initial Symptoms of Hodgkin s Sarcoma (3? cases)*

Symptoms		No of Cases
Pain		17
Abdomen	9	
Lymph nodes	4	
Chest	2	
Throat	2	
Painless enlargement of lymph nodes		8
Weakness		5
Loss of weight		5
Dyspnea		4
Cough		3
Vomiting		3
Sore throat		2
Anorexia		2

they were present in less than 30 per cent of the patients suffering from Hodgkin's granuloma

On the average, patients sought medical advice within five months of the apparent onset of their disease, yet even after this short interval the initial complaints had been almost invariably supplemented by many others and during

TABLE 4 *Symptoms during Course of Hodgkin's Sarcoma*
(32 cases)

SYMPTOMS	NO OF CASES
Loss of weight	26
Fatigue	23
Pain	21
Dyspnea	16
Anorexia	14
Cough	14
Edema	13
Fever	8
Constipation	7
Vomiting	7
Epistaxis	4
Hematuria	3
Jaundice	3
Night sweats	3
Chills	3

the course of the disease still further symptoms reflected the rapidly invasive and malignant character of the tumor

The disease runs an insidiously rapid course even though the initial response to x ray therapy may have appeared to be good Fatigue and rapid loss of weight are frequent The majority of patients develop pain referable to the organs or tissues involved and often there is cough due to the frequent involvement of the lung Fever on the other hand is rare, by contrast its frequency in Hodgkin's granuloma is well known Symptoms and signs referable to the various organs will be discussed in more detail in a subsequent section In general it may be said that Hodgkin's sarcoma runs the course of a highly malignant neoplasm

The following cases illustrate the course of the disease

CASE 13 G P (B C H 92408), a 37 year-old man entered the hospital in October 1929 because he had had epigastric distress for the previous two months The pain was constant, radiated to the umbilicus and was greatly aggravated by the ingestion of food There had been no vomiting hematemesis, melena, or jaundice There were no other symptoms of importance, and the past history was irrelevant

On physical examination a freely movable mass the size of an orange was felt in the epigastrium In each axilla and in each side of the neck were several firm lymph nodes 4 to 5 cm in diameter The spleen was felt 3 cm below the costal margin There were no other abnormalities of note The temperature was normal The red-cell count was 4 000 000, the hemoglobin 92 per cent and the white cell count 25 000, with 75 per cent polymorphonuclear neutrophils 23 per cent lymphocytes and 2 per cent monocytes Biopsy of one of the axillary lymph nodes showed Hodgkin's sarcoma

Six hundred roentgens of x ray therapy was given to the abdomen and to the nodes in the axilla and neck Two weeks later, neither the epigastric mass nor the superficial lymph nodes could be felt The response to radiation was dramatically satisfactory, and for six months the patient felt perfectly well In April 1930, however, he returned to the clinic and enlarged lymph nodes were found in the cervical, axillary, inguinal, and popliteal regions No abdominal mass could be felt. Six hundred roentgens of x ray therapy were given to each involved area, but there was little, if any, subsequent improvement in the patient's condition, in spite of this dosage and subsequent additional x ray therapy Indeed, he soon began to complain once more of severe epigastric pain, especially after meals, and of vomiting, weakness, and marked loss of weight

In August 1930, the patient was readmitted At that time, there were in each side of the neck and in each axilla firm lymph nodes 10 cm in diameter that were neither fixed nor tender The spleen was found to be 5 cm below the costal margin, and the liver was barely palpable on deep inspiration The red-cell count had fallen to 1,230,000 and the hemoglobin to 35 per cent The white-cell count was 2550, with 90 per cent polymorphonuclear neutrophils, 8 per cent monocytes, and 1 per cent lymphocytes The urine examination was negative

From then until his death 3 weeks later, the patient ran an irregular fever to 100°F and the pulse gradually rose from 90 to 130 The right leg became edematous, presumably from pressure of lymph nodes in the inguinal region, and in the right parietal bone of the skull there developed a palpable defect. X ray examination showed a large erosion of the skull in this region Many petechiae appeared in the skin of the chest and abdomen and in the mucous membranes of the mouth The patient failed steadily and died on 20 August 1930, just a year after the appearance of his first symptom

Autopsy showed Hodgkin's sarcoma involving the retroperitoneal, mesenteric, mediastinal, cervical, axillary, and inguinal lymph nodes, as well as the spleen, liver, kidneys, pancreas, adrenal glands, duodenum, ileum, colon, lumbar vertebras, and skull

CASE 14 P C (H H 24-806), a 49 year old man, was first seen in June 1924, at which time he complained of pain in the throat Two and a half months before entry he had had frequent sore throats Otherwise, the history was noncontributory

On examination, the right tonsillar fossa was found to be occupied by an ulcerated tumor 6 cm in diameter It was not bleeding A moderately large, firm lymph node was palpable beneath the angle of the right mandible No other abnormalities were noted on physical examination The patient was instructed to return one week later for biopsy and further study, but he did not reappear until September, three months afterward In the interim, his sore throat had recurred at irregular intervals without any specific treatment Examination showed in the right tonsillar region a tumor that extended high up into the nasopharynx No lymph nodes were felt in the neck There were no other abnormalities The red-cell count was 5 600 000, the hemoglobin 95 per cent, and the white-cell count 5600, with 55 per cent polymorphonuclear neutrophils, 37 per cent lymphocytes, 5 per cent eosinophils and 3 per cent monocytes A biopsy was performed, and the lymph node removed showed all the characteristics of what we now call Hodgkin's sarcoma

In November 1924 8 radium seeds of 1 m c each were implanted in the

tumor, and within six weeks it had completely disappeared The patient remained asymptomatic for six months

In June 1925, he again developed a sore throat, and the left tonsil was found to be enlarged and ulcerated Implantation of radium seeds (4 of 1 5 m c each and 2 of 1 m c each) resulted in rapid shrinkage in the size of the tumor In September of the same year, a mass of lymph nodes was palpable in the left side of the neck. One so called 'suberythema dose' of high voltage x ray was given over this area For the next sixteen months, the patient felt perfectly well and did not report to the follow-up clinic

In February 1927, he returned, complaining of recent difficulty in breathing, severe headache, and a painful mass in the neck The pharynx appeared normal, but there was a bloody discharge from the almost completely obstructed nasal passage, and a hard, walnut sized lymph node was found in the right side of the neck An x-ray film of the chest disclosed enlarged mediastinal lymph nodes High voltage x ray therapy was given to the thorax and neck, without any beneficial effect The development of deafness, diplopia, right exophthalmos, and finally blindness bore witness to the rapid extension of the neoplasm within the skull The patient died on 22 April 1927, just three years after the first symptom

Autopsy showed a tumor having the histologic features of the condition now referred to as Hodgkin's sarcoma, which was primary in the right tonsil There was direct extension to the nasopharynx, sphenoidal sinus, right orbit, right temporal bone, pituitary gland, and dura mater Metastases were found in the pancreas and mesenteric lymph nodes

CASE 15 J C (B C H 974896), a 53 year-old woman was admitted to the hospital on 14 February 1940, with the chief complaint of 'gas on the stomach' The past history was entirely noncontributory For three weeks prior to admission, she had noted that during or immediately after meals she felt 'bloated,' and there had been almost constant nausea Anorexia had been extreme, and she had grown progressively weaker

Physical examination revealed several enlarged, rubbery lymph nodes behind the left sternomastoid muscle Otherwise there were no notable abnormalties Gastric analysis showed absence of free hydrochloric acid and both the gastric contents and the stools gave a strongly positive guaiac reaction The red cell count was 5,100,000, the hemoglobin 71 per cent, and the hematocrit 37 The white cell count was 4600, with 68 per cent polymorphonuclear neutrophils, 10 per cent lymphocytes, 17 per cent monocytes, 4 per cent eosinophils, and 1 per cent basophils The temperature, pulse, and respirations were normal

A gastrointestinal series showed no abnormality in the esophagus, but x ray examination of the stomach revealed a large fungating tumor arising near the cardia The mass appeared to encroach on the esophagus but caused no obstruction The remainder of the gastrointestinal tract appeared normal

The patient became increasingly short of breath and failed rapidly The lymph nodes in the neck increased greatly in size, and within a week there developed signs of obstruction of the superior vena cava Fluid accumulated in the left pleural cavity and two months after admission, 900 cc of bloody fluid was removed Anorexia became extreme, and the patient died on 19 April, a scant three months after the first symptoms

Autopsy showed extensive involvement of the greater curvature of the stomach by Hodgkin's sarcoma, with direct invasion of the pancreas and diaphragm,

massive serous effusion in the left pleural cavity, and extensive involvement of the abdominal lymph nodes

From the case histories and the discussion above, it should be clear that, in broad terms Hodgkin's paragranuloma is a comparatively benign condition, occasionally progressing to Hodgkin's granuloma, that Hodgkin's granuloma is characterized by the most protean manifestations, is usually, though by no means invariably, fatal within a few years, and, on rare occasions, progresses to Hodgkin's sarcoma, and finally, that Hodgkin's sarcoma behaves as a highly malignant, comparatively localized tumor, rapidly resulting in death

4 INVOLVEMENT OF CERTAIN ORGANS

Hilar and Mediastinal Nodes

HODGKIN'S PARAGRANULOMA

As has already been noted involvement of the mediastinal lymph nodes occasionally occurs in Hodgkin's paragranuloma and, from the limited series of cases that have been under our observation such involvement does not appear to alter the prognosis Massive mediastinal tumors do not occur

HODGKIN'S GRANULOMA

It is a frequent event in Hodgkin's granuloma to find enlargement of the hilar nodes or the development of a large mediastinal tumor' Peirce not all of whose cases were subjected to biopsy or autopsy, found in an exhaustive study of 198 cases that 38 per cent had either intrathoracic tumor or adenopathy, and he wisely noted that the roentgenographic evidence of such lesions was far greater than the clinical signs or symptoms of intrathoracic abnormality indicated

Of 174 cases that were carefully followed at the Pondville Hospital and the Collis P Huntington Memorial Hospital 90 (52 per cent) had enlargement of either the hilar or mediastinal nodes, and in 26 of these the mass was sufficiently large to be dignified by the adjective 'massive,' for it involved, at one time or another, well over half the diameter of the chest In general, involvement of these nodes may be found at any time of life, although there is a tendency for the more massive tumors to develop in patients under thirty years of age

Implication of the mediastinal and hilar nodes, although usually an early accompaniment of Hodgkin's granuloma may occur at any time during the course of the disease In 36 per cent of 90 cases in the present series with mediastinal involvement, it was found simultaneously with the apparent onset of the condition, in another 38 per cent, it appeared within less than a year, and in but 13 per cent had the fundamental disorder been outwardly manifest for over three years before the development of the mediastinal tumor Such facts indicate clearly the necessity for roentgen ray study of the chest when the patient is first seen, even though there are no symptoms or signs even remotely suggesting such lesions

It is noteworthy that in only 1 case was there evidence during life of an intrathoracic mass without coincident or antecedent peripheral lymphadenopathy

This fact should be of considerable value in the differential diagnosis of mediastinal Hodgkin's granuloma from aneurysm of the aorta and from benign tumors amenable to surgical removal and indicates the wisdom of searching with meticulous care for enlarged lymph nodes especially in the neck and axillas in the presence of mediastinal tumor

In the case of a 43 year old man who died of lobar pneumonia autopsy showed involvement of the para aortic and peribronchial lymph nodes without the slightest evidence of Hodgkin's granuloma elsewhere The diseased nodes were markedly sclerotic and showed evidence of spontaneous healing This case indicates the possibility of primary involvement of the mediastinum and we have previously pointed out in the discussion of the pathological aspects of the disease that primary mediastinal involvement appeared in 9 of the autopsied cases

The symptoms or signs that may properly be attributed to involvement of the mediastinum are summarized in Table 1 It will be seen that dyspnea occasionally extreme and cough often harassing and persistent were the most frequent symptoms Pleural effusion clubbing of the fingers and cyanosis were the most frequent signs but it was not always clear whether the mediastinal involvement was solely responsible for in a considerable number of cases there was coincident involvement of the parenchyma of the lung furthermore some of the

TABLE 1 *Symptoms Referable to Enlarged Mediastinal Nodes in 90 Cases of Hodgkin's Granuloma*

SYMPTOM		NO OF CASES
Dyspnea		48
Cough		47
Pleurisy with effusion		23
Serous	17	
Sanguinous	5	
Chylous	1	
Clubbed fingers		8
Cyanosis		7
Hemoptysis		5
Enlarged superficial veins		4
Dysphagia		3
Hiccoughing		1
Hoarseness		1
No symptoms		18

symptoms listed may well have been due to concomitant pathologic lesions not necessarily located within the chest

It is especially noteworthy that pleurisy with effusion frequently accompanies mediastinal involvement In such cases the attendant physician should not only remove the fluid but should subsequently search carefully for evidence of hilar or mediastinal nodes so that appropriate x ray therapy may be instituted if necessary

In certain cases the mass can be outlined by percussion anteriorly or gives rise to D'Espine's sign posteriorly but it is often difficult to detect even a large mediastinal tumor by physical signs alone It is furthermore necessary to remember that early involvement of the hilar or mediastinal lymph nodes may be

completely masked, in the frontal plane, by the normal shadow of the heart and great vessels. Lateral or oblique views capable of visualizing the anterior and posterior mediastinal spaces should therefore always be taken. In the early stage, there is only an increase in the hilar shadows. Later, there is obliteration of the normal outlines of the supracardiac shadow or a blocking out of the normally aerated substernal or retrocardiac space. As the process extends still farther, there appears a homogeneous dense shadow, usually bilateral, with outlines that, as a rule, are sharply demarcated from the surrounding lung parenchyma, although there may be direct involvement of the lung parenchyma as well, and although in certain cases atelectasis of part of a lobe—particularly the lower—is brought about.

In some cases, the contour of the tumor is that of a truncated cone, in others, the mass is irregularly lobulated, and, more rarely, semicircular shadows project from the hilar region. On the basis of the x ray findings alone, it is often impossible to differentiate mediastinal Hodgkin's granuloma, bronchiogenic carcinoma and aneurysm of the aorta, and we have seen a case in which a cervical lymph node showed on biopsy Hodgkin's granuloma, whereas autopsy showed a large bronchiogenic carcinoma close to the hilar region. Of considerable value in differentiating tumor from aneurysm is the fact that in the former there is frequently a homolateral elevation of the diaphragm, a sign rarely seen in the presence of an aortic aneurysm.

It is noteworthy that in 20 per cent of the cases with mediastinal involvement there were no symptoms or signs, therefore we are forced to the conclusion that x ray examination of the chest is not only wise but necessary.

Erythema nodosum should also be borne in mind (Kerley). We have seen several patients who had considerable enlargement of the mediastinal nodes, owing to this condition, and as the enlargement may persist for a long time after the skin lesions have disappeared, the diagnosis may be difficult.

The course of the disease does not appear to be materially altered by the presence of hilar or mediastinal nodes, which usually respond surprisingly well to radiation. Of the 90 patients with mediastinal involvement in this series, 80 have died with an average duration of life after the onset of the disease of 2.7 years. The average duration in the 10 living patients is 4.7 years, and 1 patient is still in reasonably good health thirteen years after onset. In rare cases, however, the mediastinal tumor develops so fast and to such an extent that death rapidly ensues.

HODGKIN'S SARCOMA

Involvement of the mediastinal lymph nodes occurs in approximately one third of the cases of Hodgkin's sarcoma and is not infrequently associated with an extension of the process into the lung. In none of the present cases was there mediastinal involvement without coincident peripheral lymphadenopathy. It is evident from Table 2 that the symptoms are few in comparison with those of mediastinal involvement in Hodgkin's granuloma.

All patients with mediastinal involvement were over thirty five years of age. This age distribution does not differ in general from that of Hodgkin's sarcoma.

TABLE 2 *Symptoms Referable to Enlarged Mediastinal Nodes in 10 Cases of Hodgkin s Sarcoma*

SYMPTOM	NO OF CASES
Dyspnea and cough	7
Sanguinous pleural effusion	1
None	2

Mediastinal involvement usually occurs late in the course of the disease Very rarely is it the initial sign

The nodes are usually only slightly enlarged Rarely there is massive involvement *In 1 case the process extended into the lung giving rise to dullness over* the entire right lower lobe In view of the fact that the patient was admitted with a high temperature and these signs the case was initially mistaken for one of lobar pneumonia In a second case there was extension into the parenchyma of the lung but the process was not extensive

It seems doubtful whether mediastinal involvement has any particular bearing on the prognosis of any given case

LUNGS

HODGKIN S PARAGRANULOMA

In Hodgkin s paragranuloma involvement of the lung does not occur Occasionally however there is implication of the mediastinal nodes and the occurrence of such an event as previously indicated does not necessarily imply that the prognosis is poor

HODGKIN S GRANULOMA

Evidence of involvement of the lung is not infrequent during the course of Hodgkin s granuloma and pulmonary lesions are found at autopsy with even greater frequency Peirce in a careful study of 198 cases in 85 per cent of which the diagnosis had been substantiated by biopsy or autopsy found that 14 per cent *showed roentgenologic evidence of parenchymal infiltration* without pleural involvement and noted that the lesions might simulate acute inflammatory disease pulmonary abscess tuberculosis primary carcinoma or metastatic neoplasm In the present series of proved cases followed to date or to death roentgenologic evidence of lung involvement was also found in 14 per cent As already pointed out pulmonary lesions are even more frequent at autopsy in this *series* there was involvement in 41 per cent

Verse has carefully reviewed the literature pertaining to this aspect of Hodgkin s disease and concludes that the lung is involved either primarily or secondarily in approximately one third of all cases coming to autopsy Enlargement of the mediastinal and hilar nodes may furthermore bring about partial or complete stenosis of the bronchi with consequent pulmonary atelectasis and the pulmonary signs or symptoms arising from such a sequence of events are not infrequently of greater import than those due to direct involvement of the lung Moreover it should be pointed out that not infrequently under x ray therapy

a mediastinal mass entirely disappears while the parenchymal lesions remain relatively unchanged It is possible that some of these so called parenchymatous lesions are in reality small areas of atelectasis peripheral to obstruction of a small bronchus

In very rare cases necrosis of some magnitude develops so that cavities simulating those of tuberculosis or abscess are seen Verse cites 8 such cases we ourselves have not seen this type of lesion

Invasion of the lung *may occur at any time during the* course of the disease Weber describes the case of a 73 year old woman in whom a diagnosis of bronchiogenic carcinoma had been made on clinical grounds Autopsy showed Hodgkin s granuloma involving the main bronchi on the left together with a small portion of the adjacent lung tissue No metastases even in the hilar nodes could be demonstrated Verse has collected from the literature and from his own material 10 cases in which the pathologic process was apparently primary in the lung or bronchi Admittedly however such cases are extremely rare and we *have not seen any*

In our own series pulmonary lesions were demonstrated by x ray studies as early as one month after the apparent onset of the disease and as late as twelve years after it It must be remembered however that unless routine x ray studies are carried out at fairly frequent intervals the precise time of the development of the parenchymal infiltration may be misjudged for it is obvious that many of the symptoms and signs depend not on parenchymal involvement itself but rather on enlargement of hilar or mediastinal nodes

The most frequent symptoms found in patients with parenchymal disease are dyspnea cough and fever More rarely the patient complains of pain in the chest Hemoptysis is extremely unusual and its presence should arouse one s suspicion of tuberculosis Occasionally there are neither symptoms nor signs — a fact that serves to emphasize the importance of routine x ray examination of the chest — and it is worth while to draw attention once more to the obvious fact that any of the signs and symptoms of parenchymal involvement may be occasioned by the presence of a mediastinal mass Twenty per cent of patients showing pulmonary involvement have pleurisy *with effusion Only rarely is this* effusion bloody

The x ray picture of pulmonary Hodgkin s granuloma is in no sense pathognomonic As has already been said the picture may simulate acute inflammatory disease pulmonary abscess tuberculosis bronchiogenic carcinoma or metastatic neoplasm (Peirce *et al*) and it must be remembered that pulmonary tuberculosis is a not infrequent complication of Hodgkin s granuloma

HODGKIN S SARCOMA

The lungs are involved in Hodgkin s sarcoma in approximately 28 per cent of the cases or nearly twice as often as in Hodgkin s granuloma In all cases there were cough and dyspnea which were frequently severe *Fever is not unusual* although it is rather unusual in Hodgkin s sarcoma as a whole and chills are rarely seen Conversely the presence of persistent cough generally indicates that the parenchyma of the lung has been invaded The pulmonary lesions may ex

tend outward from the mediastinum or they may resemble patches of broncho pneumonia Rarely there is massive involvement of an entire lobe

Parenchymal involvement of the lung is usually associated with involvement of the mediastinal nodes Much more rarely there are isolated areas without involvement of the mediastinum In contrast to Hodgkins granuloma pleurisy with effusion is notably rare we have seen but 1 case in which this complication occurred and in this the effusion was bloody

Gastrointestinal Tract

Hodgkins paragranuloma

Involvement of the gastrointestinal tract does not occur in this form of the disease

Hodgkins granuloma

Gastrointestinal symptoms are frequent in Hodgkins granuloma but demonstrable lesions of the alimentary canal either during life or at autopsy are comparatively rare Sherman has reviewed the literature pertaining to this interesting aspect of the subject and the reader is especially referred to his excellent paper and the earlier more detailed study of Coronini From many available articles it is difficult to be certain in many cases whether the lesions referred to are actually those of Hodgkins granuloma Hodgkins sarcoma lymphosarcoma or reticulum cell sarcoma In view of the fact that the incidence of gastrointestinal lesions as well as their treatment and prognosis differs according to the type of pathologic process present this confusion is unfortunate yet readily understandable for the histologic picture of lymphoma in the gastrointestinal tract is by no means so simple and definite as it usually is in the lymph nodes

It seems clear however that Hodgkins granuloma occasionally occurs as a primary and possibly as an isolated lesion of the alimentary canal and that secondary gastrointestinal lesions are found in the generalized disease usually rather late in the course There are few reliable statistics concerning the actual frequency of such lesions Sternberg (1936) however whose criteria for the diagnosis were clear cut and definitive found that in 52 autopsies the stomach was involved in 6 cases and the small intestine in 5 As already stated in the part dealing with the pathological aspects of the disease our experience is similar Twenty four of the 213 patients in this series had gastrointestinal symptoms at onset yet only 9 of these could subsequently be shown to have any intrinsic lesion of the stomach or bowel In 5 other cases definite intrinsic lesions were found at autopsy though during life they had not been suspected During the course of the disease such complaints are more frequent and indeed they may for a time dominate the clinical picture Anorexia abdominal pain nausea vomiting and constipation — occasionally alternating with diarrhea — were the most frequent symptoms in 174 cases followed to date or death (Table 3)

Among all these patients exhibiting gastrointestinal symptoms late in their course only 3 were shown during life to have actual intrinsic lesions of the alimentary canal In 2 cases the lesion was in the lower part of the large in

TABLE 3 *Gastrointestinal Symptoms in 174 Cases of Hodgkin s Granuloma*

SYMPTOM	NO OF CASES
Anorexia	56
Abdominal pain	37
Nausea	27
Constipation	24
Vomiting	20
Diarrhea	7
Dysphagia	4
Melena	2
Hematemesis	2

testine and responded well at least for a time, to cautious x ray therapy In the third case, the lesion was in the esophagus, and there was poor response to radiation

It is probable that such symptoms as loss of appetite, nausea, and vomiting can be attributed to the general systemic effects of the disease, and all are likely to be temporarily aggravated by x ray therapy, although often subsequently relieved by the same therapeusis It is well to advise patients that this is so

Abdominal pain seems to be caused in the majority of cases by enlarged lymph nodes pressing on sensory nerves Dysphagia may be due either to pressure from a mediastinal tumor on the esophagus or to an intrinsic lesion of that structure Extremely rarely, it is due to massive involvement of the tonsils by the granulomatous process Hematemesis was directly traceable in 1 case to a wide spread involvement of the stomach but in 2 cases in which this symptom was a prominent feature no gastrointestinal lesion could be demonstrated even after careful clinical study Similarly, melena was obviously caused by gastrointestinal lesions in 3 cases yet in 2 cases in which this symptom appeared late in the disease no cause could be found during life

In the 174 cases followed to date or to death, definite clinical evidence of lesions of the gastrointestinal tract was found in 9 cases (5 per cent) In 6 of these the lesions proved at autopsy to be primary in the gastrointestinal tract and confined almost entirely to the viscus concerned and the immediately adjacent lymph nodes so that there seems to be some justification for speaking of the gastrointestinal form of Hodgkin's granuloma The stomach was involved in 3 cases, the cecum in 2 the sigmoid in 2 and the duodenum and esophagus in 1 each

It is to be noted that in no case was there multiple involvement of the gastrointestinal tract, although in a larger series, of course, such might well be true In no case were such lesions suspected or demonstrated during life The clinical importance of these post mortem findings lies in the fact that such lesions may for some time be asymptomatic, yet the patient may die suddenly from a rupture of a gastric or intestinal granulomatous lesion This event took place in 1 patient, who was discharged apparently in good condition but died six hours later from a ruptured large intestine

Clinically, Hodgkin's granuloma of the gastrointestinal tract most frequently

simulates carcinoma, ulcerative colitis or enteritis, or obstruction of the bowel (Apfelbach) The majority of published cases have occurred in the fifth and sixth decades of life, and this was so in the present series

Coincident enlargement of the superficial lymph nodes is said to be infrequent (Sherman, Coronini) One patient had what appeared on x ray examination to be a carcinoma of the stomach There was no peripheral lymphadenopathy He was operated on later, and the stomach was found to be extensively involved with Hodgkin's granuloma

With involvement of the stomach, the signs and symptoms do not differ materially from those of carcinoma, and epigastric pain, melena, loss of weight, hematemesis, and vomiting are the most frequent ones Rarely a mass is felt Singer believes that the disclosure at operation of a soft flat, infiltrating tumor associated with isolated soft lymph nodes in the adjoining mesentery should arouse the suspicion of Hodgkin's disease He adds, however, that for a final diagnosis the microscope is indispensable With this we agree Involvement of the intestine produces symptoms that are much the same, although abdominal pain and constipation are usually more prominent than they are with involvement of the stomach Hemorrhage and perforation are rare but, as has been pointed out, may be fatal

On x ray examination the findings again are usually those of carcinoma A single case with an esophageal lesion illustrates this point

E J (H 39–583), a 59 year old man, was admitted to the hospital on 8 May 1939 The past and family histories were uneventful In April, three weeks before entry, he noticed a lump above the right clavicle This was removed at another hospital, and a microscopic diagnosis of Hodgkin's granuloma was made and confirmed by us later

Physical examination on admission showed a well developed and well nourished man No abnormalities of importance were found, other than a few bean sized lymph nodes in the right axilla The laboratory findings were essentially normal Deep x ray therapy was given, with a total of 1000 r, divided between the right side of the neck and the right axilla, and within a few weeks the enlarged nodes had disappeared

The patient remained symptom free until December, when he began to complain of difficulty in swallowing X ray studies showed an extensive irregularity of the middle third of the esophagus, and an esophagoscopy on 10 January 1940 showed a large, freely bleeding and obstructive neoplastic process at the junction of the middle and lower thirds A biopsy taken at that time showed a lesion with the characteristic picture of Hodgkin's granuloma After appropriate x ray therapy, no trace of the lesion could be found by x ray studies After several months, the patient died of unknown causes

It is impossible to say with any degree of assurance whether the esophageal lesion was primary or secondary, although the latter seems the likelier In any event it was the only lesion of the esophagus seen in the 174 cases of Hodgkin's granuloma

In 2 cases the gastric lesion involved the greater curvature In a third case, there was tremendous dilatation of the stomach owing to an obstructive lesion

at the pyloric area an unusual finding in gastric carcinoma In all there was marked reduction of the peristaltic waves over a wide area In no case was there the convoluted appearance that has been said to be characteristic

C H (B C H 828826) a 56 year-old woman was admitted to the hospital on 9 July 1936 The past history was uneventful except that she had had a chronic productive cough for many years Two months before entry, she noticed considerable weakness and fatigue and during the next few weeks she vomited on numerous occasions and lost much weight For a week before admission she had had fever and night sweats There was no abdominal pain anorexia nausea melena or hematemesis

Physical examination showed an emaciated rather drowsy woman There was a harsh rasping systolic murmur over the entire precordium heard best at the apex and transmitted up the vessels of the neck The heart was enlarged 2 cm beyond the midclavicular line There were dullness and moist rales at the bases of both lungs In the right paraumbilical area was felt a small irregular firm mass that descended freely on respiration Otherwise the physical examination revealed no abnormalities of importance

The red cell count was 2 750 000 the hemoglobin 46 per cent and the white cell count 4000 with 60 per cent segmented neutrophils 21 per cent young neutrophils 2 per cent eosinophils 5 per cent lymphocytes 5 per cent myelocytes and 4 per cent myeloblasts The stools gave a strongly positive guaiac test

The temperature was of the septic type ranging each day from 99° in the morning to 103°F at night The respirations were normal The pulse averaged 115

X ray films of the lungs showed congestion of both bases Those of the gastrointestinal tract showed that the second portion of the duodenum was irregular and mottled in appearance with a definite narrowing at the junction of the second and third portions A diagnosis of carcinoma of the duodenum was made

The patient continued to run a septic temperature became increasingly drowsy and died less than a month after admission

Autopsy (A 36–449) This showed Hodgkin's granuloma primary in the second and third portions of the duodenum with extension to the immediately adjacent mesenteric lymph nodes That portion of the jejunum immediately distal to the duodenum was necrotic, and it ruptured as the bowel was being dissected out Death appeared to have been brought about by inanition and terminal multiple pulmonary emboli

In the large intestine two types of lesions may be seen — an annular constriction and a destruction of the mucosal pattern with hypermotility and increased irritability

C L (B C H 490440) a 50 year-old woman was admitted to the hospital on 27 December 1924 A year before she had noted some loss of weight and on two occasions had passed a small amount of bright blood by rectum Two months prior to entry she noticed increasingly severe constipation alternating with short bouts of diarrhea Six weeks later there developed a severe dull pain in the right lower quadrant of the abdomen made worse by eating and on three occasions during the next month she again passed blood by rectum Physical examination revealed only a firm irregular slightly tender mass the size of a small orange in the right lower quadrant X ray examination showed

some mottling of the cecum near the ileocecal valve and the cecum was dis placed upward as if by a mass outside the gastrointestinal tract

Operation was performed on 1 January 1925 and a large mass was found involving the appendix and the cecum There were several soft lymph nodes in the adjacent mesentery The mass and the nodes were removed and an ileo colostomy was performed On histologic examination the lesion proved to be Hodgkin s granuloma At operation there was no evidence of disease elsewhere

The patient died of bronchopneumonia 2 days later Since there was no autopsy it cannot be said with any certainty that the disease was confined to the cecum and adjacent nodes although this seems probable

In patients with gastrointestinal lesions an anemia of moderate or severe grade is frequent We cannot agree that any diagnostic significance can be ascribed to the white cell count for both leukopenia and leukocytosis are en countered with equal frequency and indeed often alternate in the same patient It must be remembered however that in certain cases of carcinoma there is a marked leukocytosis often with a leukemoid cast and it is common knowledge that fever is frequent in patients with cancer Fever is frequent and was present in 4 of the 6 cases with primary disease in the gastrointestinal tract in 1 of these it was a striking feature Since fever is usually present in patients with Hodgkin s granuloma no special diagnostic importance can be attached to it

It is doubtful whether a clinical diagnosis of Hodgkin s granuloma of the gas trointestinal tract can be made with any degree of assurance although the pres ence of a lesion reminiscent of carcinoma in a patient with an unexplained septic temperature and either a leukopenia of a marked polymorphonuclear leukocytosis not readily explainable on other grounds is suggestive

HODGKIN S SARCOMA

The symptoms referable to the gastrointestinal tract particularly anorexia which is often severe occur in approximately 50 per cent of cases during life (Table 4) Constipation is not infrequent diarrhea is rare Hematemesis not al

TABLE 4 *Gastrointestinal Symptoms in 32 Cases of Hodgkin s Sarcoma*

SYMPTOM	NO OF CASES
Anorexia	14
Constipation	7
Vomiting	7
Nausea	6
Hematemesis	3
Diarrhea	1

ways explainable either clinically or at autopsy occurs occasionally As in the case of Hodgkin s granuloma gastrointestinal symptoms may occur without any lesions being demonstrable On the other hand it is extremely unusual to have an asymptomatic lesion of the stomach or intestine such as one not infrequently sees in Hodgkin s granuloma

Both clinical and autopsy findings indicate that multiple involvement of the

gastrointestinal tract is not infrequent Thus, in 6 cases with clinical evidence of gastrointestinal disease, the colon was involved in 4, the duodenum in 3, the stomach in 2, and the rectum in 1, there being multiple involvement in 3 Again, there is marked contrast to the situation in Hodgkin's granuloma, in which gastro intestinal lesions are almost invariably single

The following case illustrates the course of Hodgkin's sarcoma when the gastrointestinal tract is involved

J C (B C H 974896), a 52 year old woman was admitted to the hospital on 10 March 1940, with the chief complaint of a painless lump in the neck of two months duration In addition, she had experienced hoarseness and some difficulty in swallowing She was constantly nauseated and had no appetite, but there was no vomiting There was marked weakness She had occasional distress in the left upper quadrant of the abdomen but no real pain The past and family histories were uneventful

Physical examination showed a moderately obese woman with a rather sallow complexion There was a moderately firm mass about 2 cm in diameter in the right side of the neck Otherwise the examination showed no notable abnormalities

X ray studies of the gastrointestinal tract showed a large fungating tumor arising from the superolateral wall of the cardia Gastric analysis showed normal amounts of hydrochloric acid and a + guaiac reaction There was no anemia The white cell count and differential count were essentially normal All stools gave a +++ guaiac reaction

The patient failed rapidly and died on 20 April, less than 4 months after the initial symptoms

Autopsy This showed Hodgkin's sarcoma of the stomach with metastases to the pleura, diaphragm, spleen, liver, large intestine, pancreas, and abdominal lymph nodes

Bones

Hodgkin's paragranuloma

Involvement of the bones does not occur in Hodgkin's paragranuloma

Hodgkin's granuloma

Lesions of the bones in Hodgkin's granuloma are frequent, important, and usually serious (Uehlinger) It should be emphasized that we are concerned only with the lesions giving rise to signs or symptoms during life and usually, although not invariably, recognizable by proper radiographic technic The frequency or paucity of such lesions in no way reflects the incidence of involvement of bones as determined by complete study of autopsy material for it has repeatedly been shown that medullary lesions demonstrated post mortem may not be detected by x ray This fact does not detract from the usefulness of searching for lesions during life

The frequency of bone involvement at autopsy has already been discussed Uehlinger, dealing almost entirely with autopsy material places the incidence as high as 34 per cent, and he expressly states that he is concerned only with Hodgkin's granuloma Dresser and Spencer say One may expect to find roentgen

changes ante mortem in approximately 10 per cent of all cases of Hodgkin's disease The series from which they derived their data however included not only that condition but also lymphosarcoma and reticulum cell sarcoma Since in our experience bone lesions in the latter conditions are comparatively infrequent it is probable that the incidence in these authors series of Hodgkin's granuloma was in actuality higher than that reported

Only from a series of cases that have been carefully studied and painstakingly followed can one properly judge of the frequency of such changes We have derived our figures from the cases observed and followed at the Collis P Huntington Memorial Hospital and the Pondville Hospital In neither institution have routine bone plates been taken but each patient has been so studied clinically and radiographically that at least the majority of gross lesions have been detected during life

One hundred and thirty three cases of proved Hodgkin's granuloma have been followed to date or to death at these two hospitals only and of these 30 (23 per cent) showed during life one or more bone lesions Both Uehlinger and Dresser found the changes most frequent in the spine and pelvis Such has also been our experience (Table 5) Dresser's distribution figures on 66 cases are comparable although it should be borne in mind that in all probability not all his patients had Hodgkin's granuloma

TABLE 5 *Distribution of Bone Lesions during Life in 133 Cases of Hodgkin's Granuloma*

BONES INVOLVED	NO OF CASES
Lumbar vertebras	14
Dorsal vertebras	8
Cervical vertebras	1
Pelvis	7
Ribs	5
Sternum	3
Scapula	2
Sacrum	2
Humerus	1
Floor of orbit	1
Fibula	1
Multiple lesions	10

Age does not appear to be a factor for cases with bone lesions were distributed almost as evenly throughout the decades as the disease itself (Table 6)

TABLE 6 *Age Distribution of Patients with Hodgkin's Granuloma who had Bone Lesions*

AGE yr	NO OF CASES
0–9	0
10–19	4
20–29	5
30–39	6
40–49	8
50–59	5
60–69	2

Uehlinger believes that bone lesions occur late in the course of the disease This is not in accord with our experience, for in 30 cases showing bone involvement the lesion was found in less than one year from onset in 22 per cent, and in only 6 cases had the disease been present for over four years before the bone change was noted In 5 cases the bone lesion was the first recognizable indication of the disease, or occurred within six months after its onset Dresser and Spencer arrived at similar conclusions, for they write 'In our series of 66 cases there were 16 in which the bone lesions give rise to the presenting symptoms, that is, the bones were involved early in the course of the disease in nearly 25 per cent' Their figure may be a little too high, for there is good evidence that some of the cases they refer to were actually examples of primary reticulum cell sarcoma of bone, a condition not described or recognized as such at the time they wrote In view of the fact that primary reticulum cell sarcoma of bone is probably best treated by amputation and subsequent prophylactic radiation, it is of great importance to maintain a nice distinction between these two conditions (Jackson & Parker)

The following case illustrates the early bone lesions in Hodgkin's granuloma

M L (P 3650), a 44 year-old man, was admitted to the hospital on 24 August 1931 In the previous January he had complained of severe pain in his right hip, especially on walking The pain steadily increased, and in June he was admitted to another hospital, where it was noted that there was both cervical and inguinal lymphadenopathy A biopsy was done, and a diagnosis of Hodgkin's granuloma was made On 1 September, x ray studies showed a greatly increased hilar shadow Roentgen films revealed a large bony outgrowth from the lateral margin of the right ilium and considerable lacework like new bone formation about the upper end of the right femur in the intertrochanteric region and the upper end of the shaft There was also slight thickening of the cortex of the upper end of the left tibia, and the lumbar spine showed a slight but definite increase in the density of the body of the fourth vertebra These changes were regarded as consistent with Hodgkin's granuloma The patient failed rapidly and died 23 January 1932 (Uehlinger's Case 9 presented a similar x ray appearance)

In this case it is clear that the bone lesion first attracted the patient's attention to his condition, and it appears from the history that it occurred early in the course of the disease, if, indeed, it was not the initial lesion

The roentgen ray picture is in no way characteristic It generally simulates metastatic carcinoma, but may be confused with Ewing's tumor, osteogenic sarcoma osteomyelitis, or multiple myeloma The lesion is usually destructive, especially in the spine, where it occasionally results in the collapse of one or more vertebras As a result of this collapse there may be flaccid, or more rarely spastic, paralysis Paralysis occurred in 8 of our cases in which the spine was involved It must be remembered however, that collapse may occur without paralysis, and indeed without symptoms and, on the other hand that the vertebras may be involved by direct extension from adjacent lymph nodes and that simultaneous extension from these same lymph nodes to the dura or the epidural space with tumor formation is probably a much more frequent cause of neuro

logic symptoms than is vertebral collapse as such This has at least been our experience

It is chiefly the bodies of the vertebras that are involved More rarely the transverse processes or the spines are the site of disease The intervertebral disks are characteristically spared Occasionally the lesion is chiefly proliferative Exceptionally one sees the *Elfenbeinwirbel* or ivory vertebras so accurately described and superbly pictured by Hultén Not infrequently both new bone formation and bone destruction are present Very rarely multiple punched-out areas indistinguishable from those of multiple myeloma are seen

Pathologic fracture occurs rarely We have seen only one example and that in a rib In contrast pathologic fracture is fairly frequent in primary reticulum cell sarcoma of bone

Periosteal new bone formation may be seen alone or oftener in conjunction with medullary lesions

In the long bones the metaphyses are chiefly involved Dresser and Spencer report involvement of the shaft This we have not seen

The ribs especially those portions close to the vertebras and sternum are frequent sites of invasion The sternum may be invaded directly from an underlying mediastinal mass and it is of some practical importance that such sternal lesions seem to do exceptionally well under treatment The pelvis is oftenest involved in the region of the iliac crest or the sacroiliac joints

Unequivocal cases of Hodgkin s granuloma confined to bone have not been described

Uehlinger and others believe that abnormalities of the peripheral blood picture especially leukopenia are frequently the best indication of a bone lesion We have not found this to be so Neither the red-cell nor the white cell count altered in any material manner after the development of the bone lesion Of the 2 cases with the most extensive bone changes in this series one showed a marked polymorphonuclear leukocytosis and the other a moderate leukopenia Both had only a moderate degree of anemia even at the time of death We have seen no evidence that an eosinophilia is indicative of bone involvement as some have claimed

The most frequent symptom is pain and when one considers that the patient s attention may be drawn to his condition primarily by the bone lesion and that lymphadenopathy may be minimal at that time and therefore often overlooked the importance of the search for and recognition of early bone lesions is obvious

It is important further to recognize that pain due to bone lesions may be present for a considerable period of time before the x ray films show any recognizable change In 13 per cent of our cases with bone lesions pain was present for a period of two to twelve months before the lesion was visualized in spite of repeated x ray examinations The therapeutic implications of this observation are obvious In the presence of proved Hodgkin s granuloma the appearance of pain referable to a bony structure or a joint may properly be regarded as an indication for irradiation even though no bone lesion can be found at the time On the other hand one occasionally finds on routine x ray examination gross bone lesions without concomitant symptoms This is particularly true of the skull in

vasion of which frequently gives no other clinical evidence than the appearance of a soft tissue mass directly over the area of bone destruction Similarly, lesions of the pelvis are apt to be painless unless they involve the sacroiliac joint or the hip joint Under the latter circumstances, the pain is apt to radiate down one or both legs and be mistaken by the unwary for back strain or simple 'sciatica' Tenderness over involved bones is *surprisingly infrequent*

HODGKIN'S SARCOMA

Clinically apparent involvement of bone is comparatively infrequent in Hodgkin's sarcoma, occurring in less than 10 per cent of our cases In one case, there was a small destructive lesion in the upper end of one tibia In another, there was a localized, proliferative lesion in the upper end of the femur In still another, there was an extensive destructive process of the skull In a fourth case, there was direct extension from the pharynx into the bony structure of the antrum, causing severe and intractable pain In all the other cases, the bone lesion resulted merely in a moderate degree of pain

In our experience, the bone lesions *usually occur early in the course of Hodgkin's sarcoma* They may appear later, but in view of the fact that the majority of patients die within a year and a half of apparent onset, such observations on the time of appearance of the bone lesions are of little practical value

Skin

HODGKIN'S PARAGRANULOMA

Skin lesions do not occur in Hodgkin's paragranuloma

HODGKIN'S GRANULOMA

Skin lesions in Hodgkin's granuloma are of common occurrence (Kierland) (Goldman) Severe generalized pruritus, not infrequently resulting in marked excoriation of the skin, is perhaps the most frequent one Generalized or, more rarely, localized pigmentation occurs aside *from that due to radiation therapy* Herpes zoster, not infrequently of a hemorrhagic type and often leaving behind it an indurated scar is not unusual The more specific lesions — that is, those which on biopsy show the characteristic features of Hodgkin's granuloma — are most frequently nodular or ulcerated These may exist for a long time prior to unequivocal evidence of the disease elsewhere (Senear) Generalized exfoliative dermatitis has been reported, and we have seen 1 case with this complication

HODGKIN'S SARCOMA

In Hodgkin's sarcoma, lesions of the skin occur in approximately 30 per cent of the cases and may be extremely marked They are usually papular, and *dull red and frequently scaly, resembling* closely the lesions of mycosis fungoides Rarely there are subcutaneous lesions 1 to 3 cm in diameter *We have never* seen ulceration

Patchy or extensive erythematous *lesions are occasionally seen* Itching is extremely rare

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5 INVOLVEMENT OF CERTAIN OTHER ORGANS

THE preceding section covered the involvement of the hilar nodes lungs gastrointestinal tract bones and skin by Hodgkins disease Here the involvement of certain other organs will be discussed

LYMPH NODES

HODGKINS PARAGRANULOMA

In Hodgkins paragranuloma the peripheral lymph nodes most frequently those in the neck are invariably involved Indeed the initial symptom of the condition is almost always peripheral lymphadenopathy The medastinal lymph nodes are involved in approximately one third of the cases Unless such mediastinal involvement is massive or there are indications that the condition is progressing into Hodgkins granuloma the prognosis is not necessarily poor

HODGKIN S GRANULOMA

In Hodgkin's granuloma, lymphadenopathy in one region or another often brings the physician's or the patient s attention to the presence of the disease By far the most frequent site for lymphadenopathy at the onset is in the neck,

TABLE 1 *Initial Lymphadenopathy in 213 Cases of Hodgkin's Granuloma*

LYMPHADENOPATHY	NO OF CASES
Cervical	154
Axillary	27
Inguinal	15
Mediastinal	4
None	13

and as has already been pointed out mediastinal enlargement without peripheral *lymphadenopathy is extremely rare*

The superficial lymph nodes in one or another part of the body sooner or later are almost invariably involved, and it has already been noted that by far the most frequent initial symptom is cervical lymphadenopathy, although this may not be noticed by the patient The characteristics of the enlarged nodes have already been referred to

There is some disagreement among investigators concerning the most frequent sites of the lymphadenopathy, the source of confusion often being failure to state whether clinical or autopsy material is referred to or whether an author is record ing merely the lymphadenopathy encountered when the patient was first seen or that which may have occurred later in the course of the illness

Of our 213 cases 174 have been carefully followed to date or to death The distribution of enlarged lymph nodes as observed clinically is seen in Table 2

TABLE 2 *Lymphadenopathy During the Course of Hodgkin s Granuloma in 174 Cases*

LYMPHADENOPATHY	NO OF CASES
Cervical	149
Axillary	112
Mediastinal	90
Inguinal	73
Abdominal	33
Epitrochlear	10

In 14 patients, there were no palpable lymph nodes except *in the cervical area* at any time during life Of these, 1 is alive and apparently well twenty five years after the onset of his disease The course of the other 13 cases did not differ materially from the general average In 2 cases, the enlarged nodes were limited to one inguinal region One of these patients died after four years the other is alive, following a groin dissection, seven years after onset In 2 cases only were the lymph nodes apparently limited to the mediastinum *It is of some interest* that each of these patients died within a month of his first symptom, dyspnea

In some cases, a varying degree of cervical lymphadenopathy was present over a long period of time without causing any symptoms A sudden increase in the size of the nodes then caused the patient to seek medical advice It is impossible to say in these cases whether the condition was true Hodgkin's granuloma from the onset, whether the initial lymph nodes were merely inflammatory or whether they represented one of the precursor pathologic conditions such as Hodgkin's paragranuloma, or giant follicle lymphoma In any event, the persistence of cervical lymph nodes in adults, even if they vary greatly in size from time to time, demands much more serious attention than is often accorded it This matter has already been referred to under 'initial symptomatology' One further case may be cited here

E H P (H 29-831), a 46-year-old man, was admitted to the hospital on 25 June 1929 His mother had died of tuberculosis and his father of 'carcinoma' The past history was unimportant

In 1919, the patient noticed a small, nontender lump in the right axilla This varied greatly in size, at times being as large as a walnut and at others no larger than a bean Five years later this mass was excised by his family physician, but no further treatment was advocated and no pathological study was made The patient continued to feel well until 1928, when he noted increasing constipation and some pain unrelated to defecation, in the region of the coccyx Early in January 1929, the pain became worse and 'spread throughout the rectum' The constipation continued, and in the next six months he lost 18 pounds, although his appetite remained good

[illegible] er the sym [illegible] large, firm, [illegible] trointestinal [illegible] tive process in the sacrum probably due to Hodgkin's disease [illegible] was negative A node was removed from the right axilla and showed the typical lesion of Hodgkin's granuloma

In the course of the next two months, 1200 r was given over the sacrum and pelvic region but the patient continued to lose weight rapidly and died on 11 August No autopsy was obtained

The nature of the cervical lymphadenopathy that continued, with remissions and relapses, from 1919 to 1929 in this case is, of course, uncertain, but it is our belief that, in adults, notably enlarged lymph nodes, unless associated with obvious infection, are almost always tuberculous or 'cancerous,' and one cannot help speculating what the course of the disease would have been had a radical dissection of the axilla, followed by intensive x ray therapy, been carried out in 1919

In other cases, proved tuberculous adenitis has preceded by months or years the development of Hodgkin's granuloma in the same region This sequence of events was seen in 6 of these 213 cases

Desjardins and Ford have stressed the relation of infected teeth and tonsils to the appearance of Hodgkin's granuloma in the cervical region, but the great frequency of such pyogenic infections, the comparative rarity of Hodgkin's granuloma of the tonsil, the frequency of involvement of the posterior triangle in that

HODGKIN S GRANULOMA

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HODGKIN'S SARCOMA

In Hodgkin's sarcoma the presence of enlarged superficial lymph nodes when the patient first comes to the physician's attention is by no means so frequent as it is in Hodgkin's granuloma Indeed in nearly half of our cases such peripheral initial lymphadenopathy was absent (Table 3)

TABLE 3 *Initial Lymphadenopathy in 32 Cases of Hodgkin's Sarcoma*

LYMPHADENOPATHY	NO OF CASES
Cervical	10
Axillary	5
Inguinal	3
None	14

Peripheral lymphadenopathy is usually although not invariably present during the course of Hodgkin's sarcoma (Table 4) The very generalized peripheral lymphadenopathy so frequent in Hodgkin's granuloma is seldom seen Mediastinal lymph nodes are involved in approximately one third of the cases, although massive involvement is rare It should be recalled that the disease frequently starts in the retroperitoneal lymph nodes, and these, of course, are not readily felt during life

TABLE 4 *Lymphadenopathy During the Course of Hodgkin's Sarcoma in 32 Cases*

LYMPHADENOPATHY	NO OF CASES
Cervical	21
Axillary	19
Inguinal	15
Mediastinal	10
Abdominal	9
Epitrochlear	6

TONSILS AND NASOPHARYNX

HODGKIN'S PARAGRANULOMA

Involvement of the tonsils and nasopharynx does not exist in Hodgkin's paragranuloma

HODGKIN'S GRANULOMA

Hodgkin's granuloma rarely involves either the tonsils or the nasopharynx In but 6 of our 213 cases was there such involvement In 1 there was a large translucent mass in the posterior pharynx In the remaining 5 a tonsil was involved unilaterally by a mass described as whitish or translucent The surface was occasionally ulcerated In each case the involvement of the tonsil occurred early in the disease and was almost invariably accompanied by notable cervical lymphadenopathy This fact reflects the rapidity with which this form of the

disease and the relative frequency of the involvement of the axillary and inguinal lymph nodes seem to argue against any direct etiologic relation It is perhaps likelier that acute upper respiratory or oral infections simply light up an already existing dormant disease or bring to the attention of the patient lymph nodes already enlarged but otherwise symptomless

Axillary and inguinal lymph nodes due to Hodgkin's granuloma are more likely to be painful from their position than those in the neck but otherwise they do not differ in their characteristics Epitrochlear nodes although traditionally associated with secondary syphilis and often secondary to obscure infections of the hand are sufficiently often due to Hodgkin's granuloma to demand serious attention Indeed it may safely be said that any lymph node materially enlarged over a period of time and unassociated with infection in an adult should receive a biopsy On the other hand it is extremely unusual for Hodgkin's granuloma to occur without the presence of superficial lymph nodes at some time or another during its course We entirely agree with the following statement by Baker and Mann

> Hodgkin's disease of deep structures unassociated with superficial glandular enlargement is rare In view of the frequency with which a diagnosis of Hodgkin's disease is made in cases of mediastinal tumor of splenomegaly and so forth a diagnosis often proved wrong by subsequent events we deprecate the diagnosis of Hodgkin's disease in the absence of histological evidence obtained by biopsy of superficial lymph glands If no superficial glands are obtainable during the course of the disease the case is probably not one of Hodgkin's disease

The obvious exceptions to this general rule serve only to accentuate its importance

We have seen one case that in our experience is unique and have found no report of a similar case in the literature

In 1942 a 30 year-old man (Pv 18 42) noted a painless lymph node approximately 2 5 cm in diameter in the right side of his neck The history and physical examination were otherwise noncontributory and an x ray film of the chest revealed no abnormality *No focus of infection could be found* The lymph node was excised and because a lymph node of this size in an adult is very rarely due to sepsis unless the infection is obvious approximately 300 serial sections were cut and stained In three successive sections there appeared *the* characteristic lesion of Hodgkin's granuloma filling approximately three-quarters of a high dry field These three sections together were approximately 24 microns thick Every other section was carefully examined but none showed anything more than simple inflammatory reaction A rather heavy dose of x rays was directed to the right side of the neck The patient was free from signs and symptoms five years later This is the smallest lesion of Hodgkin's granuloma that we have seen in our series Of course it is impossible to say categorically *that the patient has no other lesion* but there is no evidence that he has

This case illustrates the wisdom of cutting multiple sections of a definitely enlarged lymph node showing chronic inflammation when there is no apparent focus of infection which might give rise to a *simple inflammatory* reaction

a mediastinal tumor and a massive effusion on the left Under x ray therapy these had subsided but the left diaphragm had remained greatly elevated Under the impression that fluid still existed a needle had been introduced into the chest by a physician unfamiliar with the patient s history the diaphragm was perforated and death resulted from hemorrhage from a lacerated spleen

In our experience pleural effusions may develop at any time during the course of the disease although they are usually late They do not appear to have any definite bearing on the prognosis

Baker and Mann describe spontaneous pneumothorax This complication we have not seen

It is generally agreed that the peritoneum is but rarely implicated directly and likewise ascites is a rather infrequent complication (Uddstromer) We have found clinical evidence of ascites in only 5 per cent of our cases and in all but 1 of these the complication was terminal and was followed by death within a month or six weeks In this single case ascites was present intermittently for a year prior to exitus but it appeared to be dependent on cardiac failure rather than on granulomatous involvement of the peritoneum In another case a massive ascites developed terminally and was shown at autopsy to have been due to alcoholic cirrhosis of the liver It is always well to remember that a patient with Hodgkin s granuloma may in addition have some other major disease Our own failure to recognize this fact has in one or two cases been unfortunate Ascites should be regarded as of serious import unless occasioned by remediable factors

We have encountered pericardial effusion during life in only 2 cases In each the fluid was hemorrhagic and death ensued shortly after its clinical recognition

HODGKIN S SARCOMA

Pleurisy with effus on is also not infrequent in Hodgkin s sarcoma In our own series it occurred in 7 (22 per cent) of the cases during life In 6 of these the fluid was grossly bloody Th s is in sharp contrast to the character of the pleural fluid of Hodgkin s granuloma which as we have said is usually serous In Hodgkin s sarcoma the effusion is usually associated with involvement of the lungs In several cases however there was no evidence during life of involvement of either the lungs or the mediastinal lymph nodes It is not improbable that in these cases there was direct implication of the pleura itself by the neoplastic process The effusions whether sanguineous serous or purulent have invariably been extremely large in amount and often have required frequent thoracenteses

Ascites occurred in only 2 cases

We have never seen pericarditis with effusion

Nervous System

HODGKIN S PARAGRANULOMA

Involvement of the nervous system is never seen in Hodgkin s paragranuloma

patients, in whom the spleen is greatly enlarged to complain of a dragging sensation in the left side of the abdomen, and occasionally an enlarged spleen causes acute pain, particularly if there is an associated perisplenitis

It is well recognized that the size of the spleen may *increase greatly in the* presence of fever, and indeed it may be palpable only during periods of pyrexia. It is not so well known that an enlarged spleen may diminish in size without any treatment whatever All in all enlargement of these organs, although frequent, does not appear to have great clinical importance, except in so far as it indicates the generalized nature of this condition

HODGKIN'S SARCOMA

In Hodgkin's sarcoma, enlargement of the liver and spleen occurred — always coincidentally — in 38 per cent of our cases Rarely, however, is there great enlargement of either organ at autopsy, and their involvement does not appear to contribute materially to one's knowledge of the future course in any given case In 2 cases, the liver extended to the level of the umbilicus or lower, and in 1, *the spleen reached nearly to the iliac crest.*

Serous Cavities

HODGKIN'S PARAGRANULOMA

Involvement of *the serous* cavities does *not occur in Hodgkin's* paragranuloma

HODGKIN'S GRANULOMA

In Hodgkin's granuloma, pleurisy with effusion is frequent Evidence of fluid within the pleural cavity was found in 35 of such of our cases as had been fol*lowed to date or to death In 8 of these, the fluid was present* bilaterally In the great majority of cases, it appears to be dependent on involvement of the mediastinal nodes, much more rarely it is secondary to granulomatous lesions of the pleura Versé was of the same opinion Occasionally, it is tuberculous in origin

In 5 of our cases, the effusion was bloody, in 1, it was chylous and apparently due to tuberculous invasion of the thoracic duct, and in 1, a colon bacillus empyema had developed as a result of a fistulous tract that perforated the diaphragm and connected the colon with the pleural cavity through a *series of necrotic* nodes All other effusions were serous

[illegible] taps and

[illegible] nount

of fluid is large and repeated thoracenteses are required [illegible] relief Under these circumstances, *the eventual subsidence* of the effusion depends very largely on the response of the hilar and mediastinal nodes to radiation therapy In this connection, one point is perhaps worthy of passing comment. The diaphragm is frequently elevated in the presence of a mediastinal tumor, and *it may* [illegible] there

the foramen magnum and beneath the right temporal lobe there was 75 cc of brownish mucopurulent fluid The pial vessels were slightly injected The brain, pons, medulla, and pituitary were normal, except that on the pia over the cortex, basal ganglia, and dorsal cord microscopical examination showed a moderate amount of seropurulent exudate Cultures of the brain and cord yielded a beta hemolytic streptococcus No origin of the meningitis was found

Symptoms referable to the spinal cord are relatively frequent (Johnsson, Weil, Allen and Mercer)

Although actual granulomatous lesions arising within the substance of the cord are extremely rare, if indeed they exist, neurologic symptoms may be produced in various ways

In the first place, epidural or subdural granulomatous deposits may surround and press on the cord Lipiodol injection demonstrated in one of our patients (O O Pv 45) a block of the spinal canal which extended from D_8 to L_2 After only a moderate dose of x ray, the block completely disappeared and lipiodol injected into the cisterna flowed freely down the entire length of the canal

Secondly, there may be pressure from lesions arising in the vertebras or from collapse of vertebral bodies that have been destroyed by the disease In 92 per cent of Weil's cases the symptoms could be traced to dural lesions or those in the spine itself Sudden death has been reported from dislocation of the diseased spine and severance of the cervical cord (MacCallum) In our series, the evidence points to bone lesions as being the most frequent source of cord symptoms

Thirdly, there may be compression or actual invasion of the vessels and lymphatics of the cord by tumor from the adjacent lymph nodes Weil in particular has stressed this type of involvement He writes

> The mechanism of the myelopathy ... can easily be explained by the mechanical obstruction of blood vessels and lymphatics supplying the spinal cord through the lymphogranulomatous tissue, either within the intervertebral foramina or outside the spinal canal ... It can easily be understood that the interruption or diminution of vascular supply of the spinal cord, if continued over a longer [sic] period of time will produce a diffuse myelomalacia, which will be the more severe the more spinal arteries are involved

Fourthly, there may be a bacterial meningitis

And, finally, there may be a toxic myelitis of uncertain nature Allen and Mercer in particular have stressed this origin of the spinal symptoms Gordon and others demonstrated that the intracerebral inoculation of rabbits with emulsions of tissue derived from cases of Hodgkin's granuloma produced signs of ataxia, muscular spasms, and paralysis Examination of the cord in such animals reveals few definite lesions The fact that in experimental animals and in some clinical cases, there is a marked disparity between the severity of the clinical manifestations and the paucity of the findings on anatomic or histologic examination raises the interesting speculation whether in man, certain cases of paralysis may not be due to some ill defined toxin derived from the granulomatous tissue The possibility cannot be denied yet extremely careful study at autopsy

HODGKIN'S GRANULOMA

In Hodgkin's granuloma, signs and symptoms referable to the cord or peripheral nerves are not unusual Actual invasion of the brain substance or cord is extremely rare (Johnsson, Ginsburg)

Cortical manifestations are infrequent Johnsson found only 8 cases exhibiting cerebral symptoms among 37 that had some involvement of the nervous system Epileptiform seizures are, however occasionally seen, and appear in practically all cases to be due to invasion of the dura So far as we are aware, there is only 1 case reported in the literature in which a granulomatous lesion was found in the substance of the cortex Von Hecker and Fischer describe in some detail the case of a 32 year old man suffering from what appeared clinically to be widespread Hodgkin's disease A few days before death, he had several epileptiform seizures, followed by deep coma At autopsy there was found in the region of the centrum semiovale a cherry sized granulomatous focus that showed a histologic picture extremely suggestive of Hodgkin's granuloma Even in this case, however, some question may be raised whether the cortical lesion was actually Hodgkin's granuloma, for earlier biopsy of an axillary lymph node had shown small round cell sarcoma and according to the authors themselves, many of the involved organs failed to show a clear cut histologic picture Johnsson has been erroneously quoted in the literature as describing cortical lesions, but he specifically points out that in no case other than that of von Hecker and Fischer was there any histologic evidence of involvement of the brain substance Among our patients, there was 1 who exhibited, terminally, signs of increased intracranial pressure, choked disks, rotatory nystagmus, progressive coma, and death Unfortunately no autopsy was obtained Terminal headache, convulsions, and coma are frequent, their cause is obscure One patient died in coma following the rapid development of a meningitis

W A (B C H 346957), a 35 year old man, was admitted on 22 November 1916 In 1911 he noticed enlargement of the lymph nodes in the left side of the neck and the left axilla For the next five years, the swellings gradually increased in size, particularly during the winter months In the month of admission he [illegible] of the abdomen His general condition remained good [illegible] mph nodes in the left [illegible] nd in the right pleural cavity, and ascites was also present The veins over the lower abdomen were enlarged The temperature, pulse, and respirations were normal The red cell count was 5 400,000, the hemoglobin 75 per cent and the white cell count 3 500, with 50 per cent neutrophils, 15 per cent lymphocytes and 35 per cent monocytes The platelets were normal The patient was comfortable and up and about the ward

Six weeks after admission, the patient suddenly screamed and fell to the floor Thereafter there was deepening coma, and the temperature rose to 105°F. There were no pupillary changes and no paralysis Death occurred on 5 January 1917

Autopsy Post mortem examination showed Hodgkin's granuloma of the cervical and axillary lymph nodes and of the spleen central necrosis and regeneration of the liver, ascites, bloody fluid in the pericardial sac and acute meningitis In

slow but continued By June 1936, a year after the paralysis set in, he was able to walk with crutches, and by October of the same year he could walk without assistance His general condition was good Sensation had become normal, and the only abnormal neurologic finding was that both knee jerks and ankle jerks were hyperactive From July 1935 to October 1937, he had received a total of 4300 r (250 kv machine) to the dorsal spine In September 1937, he developed a broad band of herpes zoster corresponding to the distribution of the fourth thoracic spinal nerve on the right After three weeks, this cleared, leaving a broad scar, as herpes usually does when due to Hodgkin's granuloma

The patient was able to return to duty as a sergeant in the police force, and although his legs were somewhat weak, he remained active until his death by accident in May 1939, nearly three years after the onset of the paralysis

No autopsy was performed in this case, and the cause of the symptoms must therefore remain a matter of conjecture It is probable, however, that granulomatous tissue had extended from the para aortic nodes through the inter vertebral foramens to surround and compress the cord, and this supposition is somewhat strengthened by the development of the herpetic lesion in the upper dorsal region, for it has been suggested by many that herpes in Hodgkin's granuloma is due to pressure on the spinal roots by granulomatous tissue

In this case, no gold sol curve was done on the spinal fluid, nor have we seen any such determinations reported in the literature In other cases in this series, however, in which there was paralysis associated with Hodgkin s disease or some other form of lymphoma, the spinal fluid has usually shown a midzone curve suggestive of syphilis or early multiple sclerosis Under x ray therapy, the curve has usually flattened out or shown a tendency to less marked midzone rises

In 5 of our other cases in which there was paralysis of the legs, there was marked destruction of the thoracic and lumbar vertebras, and it seems reasonable to assume that the paralysis was due either to pressure on the cord from collapsed vertebras or to pressure from surrounding granulomatous lesions that had coincidentally invaded the vertebras There was, however, no autopsy confirmation of this supposition In 2 cases, paralysis was secondary to meningitis In 1 of these, a pyocyaneus bacillus meningitis apparently originated from a fistulous tract extending through necrotic lymph nodes from the intestine to the spinal canal In the second, there was a torula meningitis of uncertain origin

Symptoms referable to peripheral nerves are frequent Abdominal pain often seems to originate in this fashion, perhaps owing to pressure on dorsal roots Less often, there is pain in the face, neck, arms, or legs Herpes zoster is a not infrequent complication and usually leaves a scar after its subsidence Exophthalmos and enophthalmos are occasionally encountered Rarely the cranial nerves are implicated (Conybeare)

HODGKIN'S SARCOMA

Involvement of the central nervous system in Hodgkin's sarcoma is not frequent We have seen 1 tumor primary in the cerebrum and 2 cases involving the cerebellum, but unfortunately the post mortem examination in each of the latter 2 was limited to the head

would be necessary to rule out invasion of the dura or epidural space and lymph nodes pressing on afferent blood vessels It has recently been demonstrated that the Gordon phenomenon is due to the presence of eosinophils (Turner *et al*), and in this connection, it is worthy of note that in both the cases described by Allen and Mercer, there was an eosinophilia, amounting in 1 case to 78 per cent

Ten of our 174 cases, on which we have complete clinical data, showed evidence of paralysis of the legs In 8, the paralysis was flaccid, in 2, it was spastic. In all 10 cases, there was diminution or absence of tactile sensation, and there was some disturbance of the rectal and vesical sphincters In all the cases, the point of origin appeared to be in the dorsal segments In Weil's series, the dorsal region was involved in 80 per cent, the cervical in 16 per cent, and the lumbosacral in 4 per cent Weil regarded paralysis as a late and almost invariably fatal complication In over 80 per cent of his collected cases, the patients died within three months after the appearance of the neurologic symptoms, and none survived more than a year after the onset of the paralysis That the prognosis is not always so grave, however, is attested by the fact that 3 of our 10 patients survived more than a year after the paresis or paralysis had set in, and 1 was alive and in comparatively good health four years later

J C (H J 1–30), a 35 year old policeman, in the early part of 1930 noted enlarged painless lymph nodes in the left side of the neck A biopsy at that time showed the typical picture of Hodgkin's granuloma X ray therapy was instituted, and the nodes promptly subsided In 1933, the patient developed a mediastinal tumor and a left sided pleurisy with effusion Under x ray treatment and after several chest taps, the mediastinal mass subsided and the fluid disappeared He remained in fairly good health

Early in July 1935 the patient suddenly developed weakness and numbness of both legs A few days later, he became completely paralyzed from the waist down There was no pain He had some difficulty in starting the urinary stream, but no incontinence The abdominal and cremasteric reflexes were absent The knee jerks and ankle jerks were equal and hyperactive There was a bilateral Babinski sign and sustained clonus Tactile sensation was markedly diminished, and pain sensation was absent below a line parallel with the nipples anteriorly and the midscapula region posteriorly Lumbar puncture showed evidence of complete block The initial pressure was equivalent to 160 mm of water. There was no rise on jugular pressure Coughing or straining caused a rise to 310 mm The spinal fluid was clear and colorless, with 2 lymphocytes per cubic millimeter The Pandy test was strongly positive No gold sol curve was done

X ray studies of the spine revealed no definite abnormalities There were numerous small shotty lymph nodes in each side of the neck, each axilla and each groin The heart appeared to be normal The left diaphragm was markedly elevated The abdomen was normal There was no fever

High voltage x ray therapy was immediately begun over the dorsal spine Within three weeks, there was less difficulty in passing urine, and tactile sensation began to return By 8 August, approximately one month after the onset of the paralysis, the patient was able to move his legs slightly By the end of August, the improvement was marked, and he was able to move his legs in all directions, though he was unable to bear any weight on them There were still bilateral Babinski signs and ankle clonus From that time on, improvement was

the basis of destruction of the middle cerebellar peduncle and the right dentate nucleus The nystagmus was best explained by involvement of the vestibular nuclei The dysarthria and dysphagia were probably pseudobulbar

This subject has been exhaustively studied by Sparling and others

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6 CLINICAL DIAGNOSIS

In the last analysis the diagnosis of any type of Hodgkins disease must rest on a properly executed biopsy It s true that in certain advanced cases of Hodgkin s granuloma w th generalized lymphadenopathy evidence of involvement of internal organs fever polymorphonuclear leukocytosis and anemia the diagnos s can be made with some degree of assurance on clinical grounds alone but even under these circumstances experience has taught us that we may be mistaken

We therefore advise the removal of a lymph node whenever feasible The node must be selected with care and with due reference to any possible surgical risks In all cases a fair sized node should be removed for the small satellites toward the periphery of an involved area often show merely non specific inflammatory

In view of the rarity of this condition it may not be amiss to include one of the case histories

P L (B C H 1049224) a 65 year old Italian was admitted on 10 September 1941 in an unconscious state He had been well until March 1941 when following a minor injury he became shaky and staggered while walking These symptoms forced him to quit work about the end of July They increased gradually during the ensuing months and in early September his speech became thick and mumbly In addition he complained of difficulty in swallowing At approximately the same time the right eyelid tended to droop He became stuporous and at times could not recognize his own family

On admission the patient was well developed and poorly nourished The pupils were equal and reacted well The corneal reflexes were bilaterally diminished more so on the right There was weakness of the right external rectus muscle so that the right eye could not be brought beyond the midline on look [illegible] bilateral horizontal nystag [illegible] The gag reflex was absent [illegible] h was dysarthric and somewhat nasal There was no evidence of weakness of the extremities Both the finger to nose and heel to knee tests were poorly executed The biceps and triceps reflexes and ankle jerks were slightly weak The abdominal reflex was *absent and there was no ankle clonus The plantar reflex was absent on the* right and present on the left There were no other notable abnormalities

On lumbar puncture the initial pressure was found to be equivalent to 60 mm of water The dynamics were delayed and the final pressure was 0 after the removal of 10 cc of fluid which contained 40 lymphocytes per cubic millimeter and 189 mg protein per 100 cc The gold sol curve was 0001233?10 The Pandy reaction was ++ Examination of the peripheral blood showed no abnormalities

The patient became progressively worse and more and more stuporous and died eight months after the first symptoms

Autopsy Post mortem examination showed that the pons as viewed from the ventral aspect was unusually broad the right half being 0 4 cm wider than the left Horizontal sections disclosed a tumor mass occupying the white matter of the right cerebellar hemisphere the right middle cerebral peduncle and the tegmentum of the pons and upper medulla on the right side The tissue there was soft and gray and was almost liquefied in the central portions There was no sharp line of demarcation between the tumor tissue and the adjacent brain tissue In the largest horizontal diameter the lesion measured 3 2 by 3 4 cm The *tumor extended posteriorly to reach the leptomeninges* of the cerebellar cortex and medially to the fourth ventricle which was distorted and almost obliterated by the enlargement of the right cerebellar hemisphere The lateral and third ventricles were dilated to about twice normal size and the aqueduct of Sylvius was also enlarged A slight but definite cerebellar pressure cone had formed The large arteries showed a slight amount of atherosclerosis The leptomeninges and dura were not remarkable The histologic features of the tumor were those of Hodgkin s sarcoma

It is probable that the right sixth and seventh nerve palsies in this case were due to invasion or compression of the abducens and facial nuclei or of the intramedullary portions of these nerves Right cerebellar ataxia appeared to be on

the basis of destruction of the middle cerebellar peduncle and the right dentate nucleus The nystagmus was best explained by involvement of the vestibular nuclei The dysarthria and dysphagia were probably pseudobulbar

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We therefore advise the removal of a lymph node whenever feasible The node must be selected with care and with due reference to any possible surgical risks In all cases a fair sized node should be removed for the small satellites toward the periphery of an involved area often show merely non specific inflammatory

changes, and it is not easy to persuade a patient to submit to a second operation for no better reason than that the first one was unsatisfactory. Similarly, a lymph node already subjected to irradiation should be avoided unless there is an express intention to study the results of therapy, for the effect of irradiation is largely cytolytic, and the characteristic cells on which the diagnosis rests may therefore have been destroyed. It is further of the utmost practical importance that the tissue be immediately preserved in a suitable fixative, and subsequently be properly cut and stained. The histologic features of Hodgkin's granuloma cannot be identified in poorly prepared tissue, nor, for that matter, can those of any of the malignant lymphomas.

General Considerations

For convenience, the differential diagnosis of Hodgkin's disease may be grouped under three headings: patients with simple localized lymphadenopathy, those with generalized lymphadenopathy, with or without enlargement of the spleen, and those with constitutional symptoms of one sort or another, associated with little or no enlargement of the superficial nodes.

When confronted with simple lymphadenopathy apparently confined to a single region, one must consider various forms of lymphoma — that is, Hodgkin's paragranuloma, Hodgkin's sarcoma, giant follicle lymphoma, reticulum cell sarcoma, lymphocytoma, lymphosarcoma, and endothelioma — as well as tuberculosis, carcinoma, chronic inflammation, infectious mononucleosis, syphilis, leukemia, and certain other conditions.

Without biopsy, neither Hodgkin's paragranuloma nor Hodgkin's sarcoma can be distinguished from Hodgkin's granuloma. In the first of these, however, there are few, if any, systemic symptoms. The peripheral blood reveals no abnormalities, and the patient's general health is at first unaffected. The course is notably long. Most patients with Hodgkin's sarcoma are middle-aged or elderly, the disease being extremely rare under the age of thirty. The patient's health is usually disturbed, often seriously so, even early in the course of the disease. Pain and infiltrative, destructive lesions of the viscera are frequent. Fever and leukocytosis, however, seldom occur except in its terminal stages. The course is rapid and spontaneous remissions are extremely rare.

Giant follicle lymphoma is indistinguishable clinically from Hodgkin's granuloma in its early stages except by biopsy.

Reticulum-cell sarcoma occurs in the older age groups, with the significant exception of primary reticulum cell sarcoma of bone. The involved nodes are usually hard, and sometimes even stony hard and have a tendency to become fixed to the surrounding tissues. Pain is frequent and often severe. Fever and leukocytosis are rare. Localized reticulum cell sarcoma is likelier to be mistaken for carcinoma than for Hodgkin's granuloma. This is particularly true when the disease affects the tonsils or the gastrointestinal tract.

Lymphosarcoma, which is oftenest seen in childhood and in late adult life, is extremely rare between the ages of twenty and thirty years, a period of life during which Hodgkin's granuloma is frequent. The involved nodes that are the peripheral expression of lymphosarcoma are usually rather soft and of uniform

size and distribution Fever is rare except in the forms of the disease associated with acute lymphatic leukemia, in which it may be the most prominent symptom The blood, however, frequently shows an increased percentage of lymphocytes, even in the absence of frank leukemia Leukemia often accompanies lymphosarcoma or follows its development in children but is less frequent in adults

Tuberculosis is extremely difficult to distinguish from Hodgkin's disease of any type, and it must be remembered that the two diseases occasionally occur in the same patient, although rarely in the same node Redness of the overlying skin, fluctuation, caseation, and sinus formation are not infrequent in tuberculosis, whereas they are extremely rare in Hodgkin's disease It has been said that tuberculosis is prone to involve nodes in the anterior triangle of the neck, whereas Hodgkin's granuloma usually affects those of the posterior triangle, but this rule is treacherous In our experience, large single nodes in the cervical or axillary region are likely to be tuberculous The tuberculin reaction is usually positive in the presence of tuberculous lymph nodes, whereas it is almost always negative — even in high concentrations — in untreated Hodgkin's granuloma

The presence of parenchymal disease of the lung should not be taken as proof that the entire process is tuberculous, for the pulmonary lesions of Hodgkin's granuloma may closely simulate those of tuberculosis, and the two diseases may coexist in the same person Similarly, one should not be led astray by a past history of tuberculosis Not infrequently proved tuberculous lymphadenopathy in childhood is followed by Hodgkin's granuloma in early adolescence or later life The differentiation of these diseases can be easily made by biopsy

Carcinomatous nodes are generally stony hard and are often fixed to the adjacent tissues, whereas the nodes in Hodgkin's granuloma, unless they have been heavily irradiated, are, at most, extremely firm Carcinoma is likelier to cause pain, and the primary focus may be discovered to be patently cancerous It must be remembered, however, that lymph nodes involved by rapidly growing carcinoma or sarcoma may be even softer than those of Hodgkin's granuloma, and that under these circumstances, a clinical differential diagnosis may be impossible

Chronically inflamed nodes secondary to a focus of infection that is often not obvious are often seen in children but are rare in adults Small pea-sized, painless, freely movable, superficially situated nodes are, of course, often found in the cervical and inguinal regions of many healthy adults Their presence need not necessarily cause alarm, but the persistence of a notably enlarged node or group of nodes, especially if it is painless and fluctuates in size, calls for careful consideration whether there should be a biopsy If there is any doubt, a node should be removed for reassurance If there is only chronic inflammation, little has been lost, if the histologic picture is that of Hodgkin's granuloma, time has been gained It must be constantly borne in mind that in many cases, nodes affected by Hodgkin's granuloma fluctuate remarkedly under the influence of coincidental nearby infection, and that the subsidence or even the virtual disappearance of cervical nodes should not be taken as proof that they merely

represent chronic inflammation This point is well illustrated by the following case

R S (P13671) a 19 year old girl whose father had died of tuberculosis when she was a small child in 1933 noted painless lymph nodes in the left side of the neck For the next five years these fluctuated greatly in size and varied in number diminishing during the summer months and increasing during the winter particularly with the occurrence of upper respiratory infection

In January 1938 the patient developed a severe cold and the nodes increased greatly in size There was some cough and considerable dyspnea but there was no disturbance of the general health or loss of weight A node was excised and showed the typical picture of Hodgkin s granuloma X ray studies revealed the presence of a small mediastinal tumor

Whether the nodes observed in 1933 were actually the site of Hodgkin s disease must of course remain an open question Earlier biopsy would have decided this point and earlier treatment—had the nodes been granulomatous—might have aborted the disease

Infectious mononucleosis occasionally simulates Hodgkin s disease Usually however the diagnosis is clarified by the peripheral blood picture and is substantiated by the heterophil agglutination test Rarely the lymphadenopathy and splenomegaly of infectious mononucleosis remain for months after the subsidence of the acute disease Under these circumstances a careful history is important and biopsy may be necessary

Syph lis should cause no confusion if due attention is paid to the history and to the appropriate laboratory tests We have seen a case however in which following a frozen section diagnosis of lymphorsarcoma a breast amputation and axillary dissection were made the patient proving to have secondary syphilis Parenthetically it may be said that in malignant lymphoma a frozen section is an extremely slender reed on which to lean

Lymphatic leukemia rare in the twenties and thirties is accompanied by the characteristic peripheral blood picture

Rarely myelogenous leukemia is accompanied by generalized lymphadenopathy or enlarged nodes in a single region The characteristic blood picture should make the differential diagnosis clear

Tuberculosis very rarely causes generalized lymphadenopathy The differentiation of the two cannot be made clinically The possible confusion of Hodgkin s granuloma with erythema nodosum has already been referred to

In most cases with systemic symptoms Hodgkin s granuloma is accompanied even in its early stages by enlargement of superficial lymph nodes but this may not be so and in this event the diagnosis can often be made only by exclusion

Fever may be the presenting and indeed the only symptom for weeks or months which sign will later be discussed in detail Its presence particularly if it is relapsing in type and is not obviously due to one of the more usual causes should arouse the suspicion of Hodgkin s disease A careful search for enlarged

lymph nodes, especially in the abdomen, should be made, and x ray studies may reveal the presence of involvement of the mediastinum One of our patients had a relapsing type of fever for over a year prior to the development of any notable peripheral lymphadenopathy True relapsing fever due to *Spirillum obermeieri* is practically never seen in this country Undulant fever may now be diagnosed by appropriate laboratory tests We have seen a case in which the presence of fever, cardiac murmurs, progressive anemia and a gradually enlarging spleen led to an incorrect initial diagnosis of bacterial endocarditis

Rarely, Hodgkin's granuloma begins with the symptoms of an acute upper respiratory infection — namely, chills, fever, and cough Such cases are almost always rapidly fatal The tracheo bronchial and mediastinal lymph nodes, the lungs and the pleura are frequently involved at the apparent onset Usually, however, there is in addition the telltale superficial lymphadenopathy, either in the neck or in the axilla

The differential diagnosis of mediastinal masses is always difficult In our experience, a mediastinal 'tumor' due to Hodgkin's disease is generally associated with enlarged cervical or axillary lymph nodes The absence of such lymph adenopathy for any great length of time — two to six months — after the demonstration of the 'tumor' is strong evidence that it is not due to Hodgkin's disease Nevertheless, mediastinal involvement without superficial lymphadenopathy does occur, and every method of examination must be availed of for, on the one hand, certain mediastinal tumors are amenable to surgical intervention and on the other hand, certain conditions are in reality quite benign as, for instance, erythema nodosum We have followed two patients with large mediastinal masses for many months before the eventual subsidence of the nodes — without any treatment whatever In each case, we suspected from the beginning that the condition was erythema nodosum We have seen a number of similar cases in members of the Armed Forces of the United States

In the posterior mediastinum, perhaps the most frequent tumors are the neurofibromas and ganglioneuromas In the anterior mediastinum, one is more apt to find dermoid cysts, teratomas, or one of the various forms of lymphoma, especially Hodgkin's disease

Possibly the recently advocated 'needling' of the mass for diagnostic purposes will prove to be of real value It is not without danger, however

We agree with Overholt and Wilson that in broad, simple terms, a benign tumor should be extirpated and that in the case of anterior mediastinal tumors of doubtful nature, a therapeutic test of x ray should be given If there is a favorable response, further x ray therapy is indicated If there is no response, surgical intervention should seriously be considered — and promptly so

An adenomatous goiter, particularly if substernal, may cause diagnostic difficulties, for many of the symptoms and signs of hyperthyroidism such as an increased metabolic rate, tachycardia, sweating, weakness nervousness and even exophthalmos may be present both in Hodgkin's disease and in other forms of lymphoma If the question cannot be decided on clinical grounds, a determination of the organic iodine in the blood will differentiate the two conditions, for in hyperthyroidism the iodine value is two to three times normal, whereas in

Hodgkin's granuloma, even with an elevated metabolic rate, it is within normal limits (Salter)

Generalized itching, 'eczema,' weakness without other symptoms, abdominal pain, dyspnea, cough, hematemesis melena, anorexia, amenorrhea, edema, and a host of other non specific signs and symptoms testify to the protean character of the disease In the presence of such symptoms, one can do no more than sus pect that Hodgkin's disease is present and search for confirmatory evidence Since well over 90 per cent of all cases eventually show enlargement of the superficial nodes, an opportunity to prove the diagnosis is usually at hand sooner or later

Peripheral Blood Picture

Hodgkin's paragranuloma

No significant change is seen in the peripheral blood picture in patients with Hodgkin's paragranuloma

Hodgkin's granuloma

Much has been written concerning the changes in the peripheral blood picture of Hodgkin's granuloma Without question marked deviations from normal are frequent, especially in the late stages of the disease, but when one considers its protean manifestations and the number of organs that are involved, it is not sur prising that there is no uniformity of opinion about just what these changes are Out of the confusing medley of hematologic studies, however, certain facts stand out as being of practical importance There is no truly characteristic change that is, the disease cannot be diagnosed from a study of the peripheral blood alone

A variable degree of hypochromic, or more rarely normocytic, normochromic anemia develops in a large proportion of cases, particularly in the late stages of the disease In approximately one third of our cases — in all of which complete blood studies were done at each visit — the red cell count eventually fell to 3,000 000 or lower In 6 patients, 4 of whom were children it was below 1 000,000 Children seem to be more liable to severe anemia than are adults In 40 per cent of our patients under the age of twelve years, the red cell count fell below 2,000 000 in contrast to 13 per cent of the entire group The pathogenesis of this anemia is uncertain In some cases, it is apparently dependent on involve ment of the bone marrow, but that this is not invariably so is attested by the facts that in one of our patients who had by far the most extensive bone lesions, the count never fell below 3 600 000 and that in another patient who had a terminal count of 500,000, there was no evidence of bone involvement In rare cases there is hemolytic anemia of considerable severity, simulating in some re spects in so far as the peripheral blood is concerned, that of a congenital or acquired hemolytic anemia In many of these cases, there is a pseudo macrocytosis due to the presence of an increased number of reticulocytes There may or may not be alteration in the fragility of the red cells The exact explanation of this hemolytic anemia in Hodgkin's granuloma is yet to be determined Clearly,

often such lymphadenopathy is regarded as due to the infection alone, it is too infrequently recognized that lymph nodes involved by Hodgkin's granuloma but not greatly enlarged may rapidly increase in size after what appears to be a simple infection

There is a peculiar and characteristic reaction that deserves special attention — so called 'Pel–Ebstein fever' In 1887, Pel and Ebstein independently described a relapsing form of fever characterized by periods of pyrexia, alternating with intervals during which the temperature is normal or subnormal The febrile periods are marked by a gradual daily increase in temperature to 104°F or more and a subsequent equally orderly decline to normal The pulse and respirations usually follow the temperature in such a manner that when the latter is 104°F, the pulse is 120 to 150 and the respirations are 30 to 35 During the period of increased temperature, most patients feel extremely ill There follows an afebrile period of weeks or months, during which the patient may return to apparently perfect health, but sooner or later the fever returns and the afebrile intervals become shorter, and eventually the fever becomes continuous

The prognosis may with some degree of accuracy be foretold by the course of the fever The shorter the intervals between the bouts of temperature, the nearer the end When the fever becomes continuous with only slight diurnal fluctuations, death is not far off

This syndrome, although usually referred to as Pel–Ebstein fever, was accurately described by Murchison in 1870 in a case of so called 'lymphadenoma' — the British term for Hodgkin's granuloma By rights, if any man's name is to be attached to the syndrome, it should be Murchison's

MacNalty has made a special study of the fever in Hodgkin's disease

The following case is illustrative of Pel–Ebstein (Murchison) fever

F C (P 2903), a 22 year old house painter, entered the hospital on 20 January 1931 In the spring of 1930, he noted a painless lump the size of a walnut in the left side of the neck This was removed at another hospital and showed the usual histologic picture of Hodgkin s granuloma At that time there were no other symptoms, and the patient was lost sight of In October 1930, he began to have attacks of fever, malaise, and anorexia These lasted for ten days or so and recurred after an interval of apparent good health about every six weeks During each attack, the patient was confined to bed and was extremely prostrated, but between attacks he felt perfectly well Each febrile episode was ushered in by a marked sense of drowsiness and anorexia, and the temperature rose higher each night until by the end of five or six days it had reached 104 or 105°F It then gradually subsided to normal by about the fifteenth day During the febrile period there was marked anorexia, sweating, and extreme prostration As soon as the temperature became normal, the patient again felt quite well and was able to resume his daily work

Physical examination on entry showed no abnormalities except for a small scar in the left side of the neck An x ray film of the chest showed a slight increase in the mediastinal shadow There was slight anemia The white-cell count was normal but the differential count showed 90 per cent polymorphonuclear leukocytes and 10 per cent lymphocytes

Following x-ray therapy to the chest, the small mediastinal mass disappeared,

and lymphatic leukemia The number would seem to be more than could be accounted for by chance alone

HODGKIN'S SARCOMA

A moderate degree of anemia — usually hypochromic, occasionally normocytic and rarely macrocytic — is seen in Hodgkin's sarcoma In only a small per centage of the cases, however, does the anemia become extremely marked In 5 of our cases the red cell count was below 2 000 000, with a correspondingly low hemoglobin One of these patients may possibly have had a hemolytic type of anemia, for the icteric index was 50 and there was nothing to account for the jaundice Fragility tests were not done, however, so that one cannot be categorical on this point

The white cell count is usually normal, rarely it is moderately elevated The percentage of polymorphonuclear neutrophils is almost invariably high and in approximately one third of the cases there is a marked increase in the percentage of monocytes Myelocytes occur occasionally

There seems to be no definite correlation between the hematologic findings and either the organs involved or the course of the disease

Fever

HODGKIN'S PARAGRANULOMA

In patients with Hodgkin's paragranuloma fever does not occur.

HODGKIN'S GRANULOMA

Fever of one type or another, unaccompanied by sepsis or incidental and un related infectious diseases, is an extremely frequent finding in Hodgkin's granu loma Uddstromer in Sweden reported that fever was present in 54 per cent of 484 collected cases In our series, it occurred at one time or another in at least 43 per cent, it is probable that the incidence would have been higher if every patient had been constantly observed throughout the course of the disease

The fever may be of various sorts Most frequently it is as Uddstromer puts it typeless' Occasionally it is intermittent or remittent, reaching 101 to 105°F. every day More rarely, a high continuous fever is seen Such a finding is almost always terminal It is common knowledge that pyrexia becomes increasingly frequent as the disease advances

During febrile periods unassociated with sepsis, it is usual for the lymph nodes to increase in size, splenomegaly if it exists frequently becomes more marked, and the patient is generally prostrated weak and debilitated Tachycardia sometimes extreme almost invariably accompanies the fever Occasionally however, one sees a patient who, in spite of a moderate increase in tem perature — 99 to 101°F — feels perfectly well and is indeed unaware of any febrile reaction and the fact that peripheral lymphadenopathy is absent or in conspicuous at the time may render the correct diagnosis extremely difficult

Infections particularly those affecting the upper respiratory tract are prone to cause coincident enlargement of lymph nodes close to the affected area Too

Treatment

HODGKIN'S PARAGRANULOMA

It is difficult to give advice on the treatment of Hodgkin's paragranuloma In view of the apparently localized nature of the disease in many cases and the excellent results of surgery in 2 of our cases, it seems reasonable to advocate radical dissection, followed by irradiation whenever the condition seems to be sharply confined to a readily accessible region It must be pointed out, never theless, that there have been recurrences in 3 of 5 cases in which surgical excision was practiced, and this fact indicates that excision should be followed by pro phylactic irradiation Of the 5 patients who have been subjected to this routine, one is alive and entirely free from signs or symptoms thirty five years after the onset of her disease, and the other, having remained symptom free for twenty five years, developed Hodgkin's granuloma and died three years later If radical dissection does not appear to be warranted fairly heavy doses of x ray are indicated provided that not more than one area is involved

HODGKIN'S GRANULOMA

There is no specific treatment for Hodgkin's granuloma, nor is there likely to be one until its cause has been found There are, however, a number of therapeutic measures that may be expected to prolong life and that will certainly alleviate the symptoms, often for a long period of time

Three points should be borne in mind First, in the great majority of cases by the time the patient is first seen, the disease has affected more than one organ Second, virtually every organ and tissue may be involved sooner or later, and the utmost diligence must be exercised by the clinician to discover as early as pos sible any involvement of internal organs, so that appropriate therapeutic measures may be promptly instituted Third, the disease may begin insidiously in an isolated and localized focus, and it is in all probability a circumscribed process at onset This at least is our opinion although we recognize that it is not shared by many students of the subject In short, we believe that Hodgkin's granuloma has its origin in a single isolated focus, often unfortunately, internal and spreads insidiously, although rather rapidly, eventually involving many organs

It is thus clear that if one is to have any hope of actually curing the condition it must be discovered in its earliest stages and be promptly treated with the utmost energy It is equally clear that both the clinician and the radiologist must constantly be on the lookout for evidence of involvement of internal organs and must not content themselves with the gratifying results of treatment directed solely to superficial lymph nodes which are in most cases merely the visible expression of an internal lesion This point has become increasingly obvious in recent years

A biopsy should be performed prior to therapy in all cases in which it is feasible Unless this is done, and unless the removed lymph node is properly fixed and stained one cannot be certain of the diagnosis, nor can the ultimate results of any form of therapy be accurately judged Furthermore, a careful and complete physical examination, together with routine blood studies and x ray ex-

amination of the chest, should be done in all cases at the first visit Additional x ray or laboratory studies may be indicated in specific cases

The most valuable therapeutic *measure is irradiation* On this point all are agreed but there is no consensus concerning the best method of applying it Indeed it is clear that in a disease showing such diverse and protean manifestations and running such an unpredictable and variable course, this is almost inevitable The treatment must necessarily be adapted to the individual patient, the results of therapy can be adjudged only over a long period of time and with due regard to the varied manifestations of the disease

There are various schools of thought regarding the proper type of irradiation, and one may choose for oneself that which seems the most logical, the most promising and the most suitable

Gilbert has covered this entire subject with care, and to his article the reader *is especially referred An advocate of high voltage x ray, he recommends* wide irradiation of the regions patently invaded, as well as those suspected of invasion and contends that it is essential to irradiate widely enough to be reasonably certain of subjecting the entire involved regions to the action of the rays In consequence of his belief that local recurrences begin in granulomatous islands subjected to inadequate irradiation his initial doses are relatively large Panteleoroentgen therapy is in his opinion, of more harm than good

Sixteen of Gilbert's 52 patients so treated were still alive at the time of his report of these 9 (17 per cent of the total) had survived five years or more and 3 had survived for ten years or more

In recent years, our own therapeutic approach has been similar to that of Gilbert *A 250 kilovolt machine is used Each area involved or suspected* of being involved is treated through a portal of sufficient size to embrace the entire field in fractionated doses until the required amount has been given It is probably best to give comparatively small doses to any given area if the disease is widespread but many authorities believe that large, heavy doses should be given if the condition appears to be confined to one region No further irradiation is resorted to unless there is a recurrence

Recently, we have in certain selected cases used a supervoltage (1000 kilovolt) x ray machine It is too early to come to any conclusion concerning the relative merits of this method of irradiation All patients are seen at frequent intervals – two weeks to three months – and great diligence is exercised in attempting to discover by one means or another, any new focus of disease Any [illegible] rded as be [illegible] This is an important part of the treatment *irrespective of the exact type of irradiation* used Of the 35 patients in our series still alive 17 (47 per cent) have survived for five years or more Sixteen per cent of the patients in the entire series who were subjected to and adequately followed systematic treatment *survived* for five years or more

It is our belief that the internist and the radiologist should care for the patient conjointly and that all details of x ray therapy should be left to the *radiologist* No matter what type of x ray therapy is used – and it is obvious that competent

authorities advise varying methods of attack — certain practical points should be borne in mind In the presence of anemia (3 5 million or less), it is probably best to transfuse the patient with blood until the red cell count is 4 0 million or above before x ray therapy is instituted

Extremely large mediastinal masses must be treated with great caution for not infrequently they are extremely radiosensitive, in which event too rapid destruction by excessive amounts of x ray may result in the organism's being flooded with products of necrosis, which may bring about highly toxic manifestations or even death

The acute form of Hodgkin's granuloma, accompanied by high temperatures, an elevated white cell count, and the signs and symptoms of an acute infection, must be treated with great care and conservatism A rapid rise in temperature calls for temporary cessation of therapy The situation is somewhat analogous to that seen in acute leukemia

The presence of active tuberculosis contraindicates irradiation of the lungs and mediastinum in the usual doses, as does renal insufficiency, especially if associated with nitrogen retention We know of no good evidence, however, that x ray therapy, per se, will bring on acute disseminated miliary tuberculosis

The presence of unexplained fever, vague gastrointestinal disturbances, fleeting abdominal pains, generalized itching, or a persistently elevated white cell count, with an increase of polymorphonuclear leukocytes, usually indicates the presence of diseased lymph nodes deep in the abdomen or in the para aortic region, and irradiation of these areas often causes a remission of the symptoms

We have been increasingly impressed with the wisdom of relentless treatment, even in the face of what appear to be overwhelming odds Of course a point is reached when further irradiation is fruitless and even harmful but this does not usually occur until after many courses of treatment, and it is remarkable what may be accomplished in the relatively early stages of the disease even though the patient may seem at the time to be at death's door Many patients have rapidly and markedly failed, only to return to comparative health when hospitalized, transfused and given appropriate irradiation Gilbert cites such a case from his own practice

To obtain the best co-operation and thus the best results, it is wise to give the patient a general idea of what may be expected of x ray therapy It is not necessary to name the disease, it would obviously be unwise to picture the final outcome, and it is unnecessary to dwell on details It is, however, proper to point out that the outward manifestations of the disease will diminish or even disappear, but with a warning that the same disease process may subsequently reappear in another place and that any untoward sign or symptom should be immediately reported Only thus and by repeated routine examination can one hope to keep the disease in abeyance

The question of marriage and pregnancy is, of course, of great importance Both should probably be advised against but as Gilbert says 'these events occur in spite of us' If pregnancy should take place, it is necessary to decide whether it should be terminated This question cannot be categorically answered Three of our patients have become pregnant One, a multipara, was aborted at

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though he had lost some weight—but he complained of intense pain in the lumbar region, particularly on the right side

Physical examination showed a marked lumbar scoliosis on the left side and intense contraction of the lumbar spinal muscles on the right side X ray films showed a destructive process of the bodies and transverse processes of the first and second lumbar vertebras There was a slight degree of vertebral collapse Six hundred roentgens was given over the involved area, and the pain completely disappeared In January 1937, there was some return of the pain but complete relief was again obtained after the administration of 400 r to the lumbar region

In May 1937, the patient again complained of considerable discomfort in the lumbar region, and x ray examination showed an increase of the destruction of the first and second lumbar vertebras Nine hundred roentgens was given over the involved area, and in October there was evidence that new bone was being laid down in the bodies of the vertebras and that fingerlike processes of new bone were reaching out into the soft tissue to bridge the existing defect The radiologist noted that there appeared to have been an arrest of the process and a laying down of calcium deposits in the ligamentous structures surrounding the lateral portions of the first and second lumbar vertebras on the left

The general result was that, in spite of the bone destruction, there was a partial and fairly effective ankylosis of the spine Nine hundred roentgens more was [illegible] was able to [illegible] the marked [illegible] complained, [illegible]

By October 1939 the lesion of the lumbar spine had extended to include the body of the twelfth dorsal vertebra There was, however, no increase in symptoms, and the patient was still active in athletics eight years after the initial symptoms and three years after the demonstration by x ray of a destructive process [illegible] y in 1940, there developed [illegible] which gradually increased [illegible] es The patient remained cheerful, however, and his physical activities were limited solely by the pain, which became so severe in the fall of 1940 that a dorsal cordotomy was performed The operation was entirely successful in so far as relieving the pain was concerned, but the patient failed rapidly and died in December, nine years after the initial symptoms

In addition to irradiation, three therapeutic adjuvants must be considered. blood transfusions, general care, and surgery

Some authors object to transfusions and believe that they are rarely of benefit and may even be harmful (Wallhauser) We, on the contrary, agree with Gilbert that they are of inestimable value, and it is doubtful whether the reactions to which some authors have drawn attention would occur if careful attention were paid not only to the group, but also to the subgroup of both donor and recipient This is particularly important if repeated transfusions are necessary at rather long intervals, for although, for instance, A_1B_- blood may produce no reaction on the first transfusion in an A_1B_1 recipient, the patient may gradually build up antibodies against B_- in such a manner that subsequent transfusions even from the

her own request She was alive and free from symptoms three years later The other two, both primiparas, gave birth to normal babies, and each was well one and two years later, respectively, both children remaining well Gilbert has had a similar although more extensive experience The ultimate fate of the offspring cannot, of course, be foretold, but the present data seem to justify allowing pregnancy to go to term provided that one or both of the parents realize the potentialities

In assigning to the fundamental disorder signs and symptoms that may properly be attributed to it, enthusiasm must be tempered with a modicum of knowledge of general medicine One of our patients, a sixty-year old Armenian, with 'small Latin and less Greek' said that he was unable 'to pass the water' What was more tempting in view of the fact that his disease was widely disseminated, than to see as a cause of this complaint a granulomatous process in the prostate and to irradiate that organ Forthwith he was indeed, 'unable to pass the water' It was with much relief and some chagrin that we witnessed a complete and lasting disappearance of his symptoms following a prostatectomy for the simple, benign prostatic hypertrophy of old age

In almost all early publications concerning irradiation, it was stated that, although the symptoms could be alleviated, life could not be prolonged It has recently become increasingly apparent that this is not the case, and we agree with Gilbert and others that the average duration of survival is prolonged. In 1923 Desjardins and Ford found that only a scant 10 per cent of their patients survived for more than five years In 1932, Holfelder and Hummell (quoted by Gilbert) reported that nearly 18 per cent of their patients had passed the five year mark In Gilbert's series, 17 per cent fell into this category

The results of irradiation vary within wide and unpredictable limits, as a rule, they are fairly satisfactory Generally speaking, however, bone lesions are less radiosensitive than are foci in other organs Lesions of the sternum, however, usually show a satisfactory response In any event, relief from pain is often striking and in some cases bone regeneration and repair have been observed That excellent results may be obtained in such cases is attested by the following case

E W (P 1933), a 20 year-old man, was admitted to the hospital on 3 January 1933 In September 1931, he had noticed a 'swollen gland' behind the left ear One month later, this became painful and other lymph nodes appeared in the left side of the neck One of these was removed, and a diagnosis of Hodgkin's granuloma was made During the next 5 years, lymph nodes appeared from time to time in the neck, axillas and groins but always diminished or disappeared after appropriate high voltage x ray treatment In addition the patient was periodically troubled by intense generalized itching, which was partially controlled by spray x ray treatment and by viosterol in large doses His general health, however, continued to be good, and he remained mentally and physically active

In June 1936, the patient complained of pain, especially on motion in the lower lumbar region This was relieved by the administration of 60 r spray to the body anteriorly and 100 r posteriorly In October of that year there were no palpable lymph nodes, and the patient's general condition was excellent—al-

though he had lost some weight—but he complained of intense pain in the lumbar region, particularly on the right side.

Physical examination showed a marked lumbar scoliosis on the left side and intense contraction of the lumbar spinal muscles on the right side. X-ray films showed a destructive process of the bodies and transverse processes of the first and second lumbar vertebras. There was a slight degree of vertebral collapse. Six hundred roentgens was given over the involved area, and the pain completely disappeared. In January 1937, there was some return of the pain but complete relief was again obtained after the administration of 400 r to the lumbar region.

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The general result was that, in spite of the bone destruction, there was a partial and fairly effective ankylosis of the spine. Nine hundred roentgens more was given, and the patient continued to be in reasonably good health and was able to control the discomfort in the lumbar region by salicylates. In spite of the marked bone lesion he was able to swim, play tennis, and ski, although he complained, with a smile, that a left hand telemark was hard to accomplish.

By October 1939, the lesion of the lumbar spine had extended to include the body of the twelfth dorsal vertebra. There was, however, no increase in symptoms, and the patient was still active in athletics eight years after the initial symptoms and three years after the demonstration by x-ray of a destructive process in the spine involving at least three vertebras. Early in 1940, there developed considerable pain in the lower back and in both legs, which gradually increased in severity and could be controlled only by opiates. The patient remained cheerful, however, and his physical activities were limited solely by the pain, which became so severe in the fall of 1940 that a dorsal cordotomy was performed. The operation was entirely successful in so far as relieving the pain was concerned, but the patient failed rapidly and died in December, nine years after the initial symptoms.

In addition to irradiation, three therapeutic adjuvants must be considered: blood transfusions, general care, and surgery.

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same donor are accompanied by violent reactions (Ham) It is our custom to transfuse patients whose red cell count is 3 000 000 or below unless they are in the terminal stages of the disease We have never seen an untoward reaction when the bloods were properly matched in both the major and the minor agglutinations

Iron in the form of ferrous sulfate may be of benefit

It is obvious that general care is of importance in any chronic condition, and this is no less so in Hodgkin s granuloma Plenty of rest ample food that is high in vitamins and the other essential elements, fresh air and sunlight within the tolerance of the patient are all of real value Not a few patients volunteer the statement that their sense of well being is greatly enhanced if they stay out-of doors in the sun

Obvious foci of infection should be removed for they undoubtedly have a provocative influence on the condition For itching, in addition to the irradiation referred to above local applications of 0 5 per cent phenol in olive oil may be tried For pain, particularly that arising from bone lesions, salicylates in full doses often produce surprisingly good results One of our patients had a destructive lesion of the lumbar spine associated with marked pain X ray therapy brought about a regression of the bone lesion but the pain, which was apparently dependent on the resulting scoliosis and muscle spasm, persisted For several years it has been controlled by large doses — 2 to 6 gm — of aspirin a day and the patient is able to live a normal and indeed active life

Our experience with cordotomy for pain has been most unsatisfactory, although there are no doubt cases in which it is of benefit In 1 case, skillful injection of the posterior roots with alcohol was followed by complete relief of pain There was no further discomfort until the patient s death a year later

The nitrogen mustards have been extensively used in the treatment of Hodgkin's disease and other forms of lymphoma Whereas some investigators believe that these compounds are more beneficial than the more conventional x ray therapy, the more conservative report of Rhoads may perhaps be taken as the best guide to their present therapeutic status Rhoads points out that toxic effects, chiefly on the blood forming organs are not rare and that "The tumor regressions induced by these compounds (even with maximum dosages) are temporary with maximal persistence rarely extending beyond several months" He also draws attention to the fact that the mustards cannot like x ray be used locally We ourselves have had no personal experience with these compounds but we should hesitate to recommend their use unless the disease had become radio resistant, and then only at the insistence of the family or the patient

It has been said that the nitrogen mustards may induce a remission of the disease after it has become radio resistant and this may well be true But those who have had extensive experience with the treatment of various types of lymphoma recognize that the degree of radio resistance or radio sensitivity varies considerably in a given patient, even though in the long run it must be conceded that the patient does become progressively more radio resistant

We have used folic acid extensively but have as yet seen no benefit accrue

The question of surgical intervention is a moot one First championed by

Yates and Bunting in 1917, it has since fallen into disrepute The great majority of writers on the subject have concluded that it is useless, some because they have seen it fail again and again, others because they have seen the rapid return of lymph nodes in the operative field, and still others because of their belief that Hodgkin's granuloma is always a generalized disease from the start – a belief for which there are no valid grounds It is true that by the time the pa tient first seeks medical advice, the process is usually widespread or at least inoperable It is also true that in many cases, the original focus is internal and therefore inaccessible, but both clinical experience and autopsy findings tend to show that the disease begins in one focus and spreads from it – slowly in some cases and rapidly in others

Gilbert writes 'Surgical procedures have shown themselves useless, they do not influence the evolution of the disease Local recurrence or extension develops shortly after operation, except in the benign local, and peripheral forms in which the lymph nodes are still movable' Baker and Mann adopt a some what more militant and optimistic attitude They cite the first and second cases in their series, in each of which there was performed surgical excision of the diseased tissues, associated with deep x ray therapy The first patient was alive and well thirteen years and the second eleven years after operation It is the opinion of these authors that when the lymph node enlargement is localized, surgical excision should be practiced and the area subsequently irradiated We share this view, with the full recognition that suitable cases are indeed rare and that even in them some hidden focus not apparent at the time of operation may frustrate attempts at cure Much has been said and written about the necessity for early diagnosis in cancer, and it is generally appreciated that in early recogni tion of this disease lies the best hope of true cure The same can be said for Hodgkin's granuloma

Two of our patients with this disease have been subjected to radical excision of cervical lymph nodes One is alive and free from signs and symptoms of disease eleven years after operation, and the other is alive and well eight years after operation Both patients were children when the initial symptoms were noticed It is obvious that in view of the extremely variable course of the disease, no conclusions can be drawn from these cases, and at best the results are only suggestive Too often, however, one hesitates, argues, and procrastinates until the time comes when it can be truthfully said that operative interference is uncalled for Too often one waits to see what will happen Too seldom does one proceed radically *Such is the early history of many incurable diseases* The para dox is that when the lymphadenopathy is still possibly amenable to complete surgical removal, it is liable to be regarded as benign whereas when it has be come inoperable, one contents oneself by saying that it always has been so

Certain authors have claimed excellent therapeutic results with Hodgkin's granuloma, confined to the gastrointestinal tract, but so far as our experience goes these patients fare badly, for in no case did a patient survive for more than eighteen months after the initial symptoms, and the average duration of life from onset to death was only nine months Patients with gastrointestinal lesions incidental to a generalized process similarly appear to have an unfavor

able prognosis, if the figures derived from such a small series may be regarded as significant

In certain cases, an epidural mass may be of such size that it greatly compresses the cord and does not respond to x ray therapy sufficiently to relieve the pressure Under these circumstances, laminectomy and removal of the mass is entirely justifiable One of our patients (M K Pv 10 44) had proved Hodgkin's granuloma and a marked spastic paraplegia Appropriate studies showed a large epidural mass compressing the cord in the high dorsal region X ray therapy did not afford relief, and the mass was therefore removed Thereafter, the compression on the cord was relieved and the patient slowly improved, though at the time of this writing (two years later) the paraplegia has returned We have seen a number of such cases in which surgical intervention was not only justified, but was followed by prompt and often rather lasting benefit

The psychologic aspects of treatment should never be overlooked If the patient is a physician, he should be told the precise diagnosis The details of the treatment and prognosis need not, and indeed should not, be dwelt on We have cared for a considerable number of doctors afflicted with Hodgkin's disease or allied conditions, and all but one have borne their disease with cheerful stoicism from beginning to end In the single exceptional case, serious family difficulties unquestionably contributed to the patient's mental undoing

If the patient is a layman it is probably best not to name the disease even though — as is usually the case — one is asked what it is Practically all patients are content with evasive answers, and rarely press the point if they are casually told that some lymph nodes are enlarged for some obscure reason and that much can be done to alleviate their symptoms The mere assurance that symptomatic improvement can be achieved almost always sets the patient's mind at comparative ease, and the initial therapeutic success tends to tide him over subsequent recurrences, even though these may be less amenable to such therapeutic measures as are available As time passes, the patient himself often comes to the realization that he is going to have the disease the rest of his life, and this recognition gradually changes to an awareness that he is sure to die of the disease. This inner awakening to the bitter truth hurts far less than would a blunt statement on the part of the attendant physician Less frequently, the patient imperceptibly — to himself — grows worse and worse, never being genuinely conscious of the impending end Still less frequently, sudden death occurs even when the patient appears to be doing well

Very rarely one encounters a patient who asks how long he will live, and means it In such cases, an entirely plausible reason is always given for wishing this exact information The absence of such a logical reason is usually sufficient evidence that the patient is not truly serious in his questioning Even so, dogmatism must be avoided, the course of the disease is too erratic For example, one young man asked how long he would live From his former physician he had learned the diagnosis When asked why he wished to know, he replied calmly that he wanted to plan his life in accordance with the prognosis He was told that he would live for one year, and at his request he was shown the evidence on which this statement was based 'All right,' he said, I will build a house —

that takes a year.' Six years later the physician who had made the prognosis received a note in which the patient remarked that the skiing was excellent in the mountains and invited him to come there for the weekend. The patient died four years later following a major surgical operation. The individual patient is not the average patient, and the rules of Hodgkin's disease are made to be broken.

It should be recognized that patients with this disease are unusually quick to grasp the significance of any remark arising from the physician's awareness that the end is approaching; indeed, they exaggerate it. In several of our cases, fear and despair has supplanted hope and a sense of security. For example, a patient who lived in a distant town had done unusually well for five years but then began to fail although without realizing it. It was suggested that he get in touch with a local physician so that there might be someone at hand who was familiar with his case. On reaching home, he telephoned his son and said, 'Well, my death warrant has been signed.' In a week he was dead. It may be argued that he would have died anyway, but this is doubtful, and at least he would have died in peace had the subject been brought forward earlier and more tactfully.

In all cases, some responsible member of the family, not necessarily the nearest of kin, must be told in lay terms the diagnosis and the probable prognosis. Even here, however, one must be cautious, for, as has been repeatedly said, each case is a law unto itself.

Ben Ames Williams has covered this whole subject very well. He says:

> To the doctor's most persistent psychiatric problem — How much of the truth shall you tell the patient? — there is no complete answer. Yet the better you know your patient, the more wisely you can solve this problem. How much of the truth will you tell a patient with a hopeless case? To be sure, you may be wrong in your diagnosis, but in what seems to you a hopeless case, will you be frank with the patient? Will you tell his family? One doctor of wide experience recently assured me that he never tells the hopeless truth. I have known two people who were killed — their deaths hastened — by being told the truth. One, an old man who had been a granite cutter in his youth, had, through a long life, been proud of the fact that he had never contracted tuberculosis. In his middle seventies he fell ill. I was with him — he was jolly, mentally himself, physically strong enough to walk and talk — when a rural doctor whom he had consulted came into the room and said flatly, 'Mr McC., you have tuberculosis.' He never spoke another rational word, and died ten days later. Another, a woman developed a progressive and incurable ailment, but her life expectancy was ten, twenty or thirty years. Told that she would never get better, she died in three months.
>
> On the other hand, I have known men who were told that their days were numbered — and who lived full and happy lives for many a year thereafter. I think of one man who was given — on condition that he mended his outrageously dissipated ways — a maximum of six months. He decided that virtue was not worth the price, and has continued his excesses through the sixteen years that have ensued since the day sentence was pronounced on him. To decide who shall be told the hopeless truth is a problem impossible of positive solution, but he who oftenest solves it correctly is the best doctor.

Fear is a poison, yet sometimes doctors seem deliberately to provoke fear. It

is as though they were completely unaware of the impact on a patient of their smallest word

It is the hard lot of the doctor to know that in the end he is always defeated, his victories at best are temporary Death he can never finally conquer But death's ally is fear and this ally the doctor can defeat Let him help the patient to conquer fear, and he will win many a skirmish, and if he can never hope to win the last grim battle, he can at least do much to rob that ultimate defeat, for his patient and for the patient's family, of the terror that is its most grievous pain

HODGKIN'S SARCOMA

The treatment of choice in Hodgkin's *sarcoma, as in other forms of Hodgkin's* disease, is irradiation, yet it must be admitted that there is no convincing evi*dence that such treatment, even when given in full doses* is of much avail Not infrequently, virtually no response is obtained, a result that in Hodgkin's granuloma is extremely rare In the presence of anemia, transfusions are helpful The fact that in most cases the condition arises in an internal organ or in the retroperitoneal lymph nodes and is thus less likely than otherwise to be diagnosed at an early stage militates still further against successful therapeusis

If the condition is discovered at an early stage, when the lesion is comparatively localized, radical surgical intervention appears to be indicated, but we have not encountered any such case

Prognosis

HODGKIN'S PARAGRANULOMA

For certain forms of malignant disease, such as osteogenic sarcoma, a maximal time of survival may be set with some degree of accuracy, and in the great majority of cases the physician may rest assured that an actual cure has been effected if the patient survives this date This situation does not obtain in Hodgkin's paragranuloma

The prognosis of this disease is comparatively good Of 28 patients followed to date 15 (55 per cent) have been alive and free from symptoms for five years or more and 5 *have survived a fifteen year period* It *is of* considerable signifi

TABLE 1 *Survival Period in Cases of Hodgkin's Paragranuloma*

	SURVIVAL TO DATE OR TO DEATH yr	NO OF CASES
Patient alive	Less than 3	0
	3–9	7
	10–24	8
	25 or more	1
Patient dead	Less than 3	5*
	3–9	6†
	10 or more	1
Total		28

* Death due to unrelated causes in 3 cases
† Death due to unrelated causes in 2 cases

cance that of the 12 patients who have died, 5 succumbed to diseases entirely unrelated to their disease, the remainder developed Hodgkin's granuloma and died *in less than ten years after onset*

HODGKIN'S GRANULOMA

Hodgkin's granuloma is generally regarded as a fatal condition, leading to death in one to three years Yet it is important to remember that the individual patient is not the average one, that the span of life from onset varies within wide

TABLE 2 *Average Duration of Disease from Onset to Death according to Age at Onset in Cases of Hodgkin's Granuloma*

AGE AT ONSET *yr*	MEDIAN DURATION *yr*	NO OF CASES
Less than 10	2 5	14
10–19	2 4	26
20–29	2 8	21
30–39	2 4	19
40–49	1 3	23
50–59	2 6	18
60–69	0 6	12
70–79	0 9	2
80–89	0 7	1
Total		136

limits, and that rarely a patient survives without evidence of active disease for so long a time that an actual cure may at least be considered possible

In Table 2 is shown the duration of life from the first sign or symptom that could properly be considered as due to the disease itself in the 136 cases of our series in which the patients died of the disease, after being followed throughout its course Three patients died of entirely unrelated causes and are therefore not included. It is apparent that the average length of life from onset to death is approximately two and a half years Uddstromer's data, based in a like manner on 494 fatal cases, are in essential agreement with ours, and Wallhauser,

TABLE 3 *Duration of Disease from Onset to Death in Cases of Hodgkin's Granuloma*

DURATION *yr*	PRESENT SERIES (136 CASES) %	UDDSTROMER'S SERIES (494 CASES) %
Less than 1	24	33
1–2	45	45
3–4	17	16
5–9	13	6
10 or more	1	0

from a review of the literature, has come to essentially the same conclusions These average figures, however, by no means tell the whole story Thirteen per cent of our patients lived for five years or more after onset, and 1 died eleven years after onset (Table 3) About 30 per cent, therefore, lived definitely longer than those in either the average or median group, and 13 per cent lived twice as long

When one considers those patients who are still alive a somewhat different picture is seen (Tables 4 and 5) It is apparent that the duration of the disease

TABLE 4 *Average Duration of Disease from Onset to Date according to Age at Onset in Cases of Hodgkin s Granuloma*

AGE AT ONSET yr	MEDIAN DURATION yr	NO OF CASES
Less than 10	5 0	5
10–19	6 0	3
20–29	5 6	9
30–39	4 3	4
40–49	5 7	6
50–59	4 8	6
60–69	3 0	1
70–79	5 2	1
Total		35

in the patients in both series is notably longer than it was in those who died Whether this is due to the statistical error of a relatively small series — 69 living

TABLE 5 *Duration of Disease from Onset to Date in Cases of Hodgkin s Granuloma*

PERIOD yr	PRESENT SERIES (35 CASES) %	UDDSTROMER S SERIES (34 CASES) %
Less than 3	22	9
3–4	28	47
5–9	44	38
10 or more	6	6

cases — or can be attributed to the increased efficacy of more recent x ray therapy is a question that cannot be answered with any degree of assurance The fact remains however that of these 69 patients 32 (46 per cent) have had their disease for five years or more and that of these 6 per cent have survived a ten year period

The question therefore naturally arises whether at the onset there are any criteria by which one can foretell the course of the disease Fifteen of our patients died in less than six months after the apparent onset and 11 survived for eight years or more 7 of these being alive and in reasonably good health for eight to twenty two years after the first symptom

If these two groups of cases examples of the prognostic extremes are contrasted certain definite points stand out The onset in the rapidly fatal cases was usually suggestive of an acute infection or indicated internal involvement Chills dyspnea cough fever abdominal pain sweating or dysphagia were seen at the very beginning of the disease and only 7 of the 15 patients had palpable superficial lymph nodes when first seen although all but two had peripheral lymphadenopathy prior to death (Table 6) In almost all cases in which cough dyspnea chills sweats and fever were present at the onset of the disease death occurred within six months One cannot of course expect this rule to hold in every case but it appears to be a helpful prognostic guide As Uddstromer

TABLE 6 *Most Frequent Initial Symptoms in Fifteen Rapidly Fatal Cases of Hodgkin's Granuloma*

SYMPTOM	NO OF CASES
Cough	9
Dyspnea	7
Superficial lymphadenopathy	7
Chills	5
Hemoptysis	2
Fever	2
Dysphagia	1
Sweats	1

points out, however, the disease process may have been in existence much longer than the symptoms indicate when it has its origin in the hilar, mesenteric or retroperitoneal lymph nodes, and the actual duration of the disease may therefore be longer than is evidenced by the available clinical data

Of the 11 patients who survived for eight years or longer and 8 of whom are now alive and in reasonably good health, 8 sought medical advice for simple, painless, localized lymphadenopathy without any associated signs or symptoms One had, in addition a certain amount of general fatigue, 1 complained of dyspnea, and 1 entered the hospital for the first time with a complaint of weakness of the legs

The contrast between these two groups is sufficiently arresting to demand attention By and large, in the rapidly fatal cases there was an onset suggestive of an acute infection whereas in those of long duration the patients presented themselves with simple lymphadenopathy, only occasionally associated with symptoms of generalized disease The more nearly a given case approaches one or another of the extremes, the more does the course run true to form

Most students of this subject agree that no definite relation exists between the onset of pulmonary findings and the progress of the disease Falconer and Leonard were unable to determine any connection between the time of onset of pulmonary symptoms and the time of death It appears however, that these authors dated the onset of pulmonary involvement from the first pulmonary symptoms, which may well have been due to mediastinal or hilar node involvement, rather than to actual implication of the parenchyma Similarly Peirce et al state that the roentgenological appearance offers no criteria for prognosis

Our own experience has been somewhat more definitive No patient in whom pulmonary lesions were demonstrated at autopsy lived for more than eight months after these changes had been discovered during life, and the great majority died within three months Three patients who gave x ray evidence of pulmonary invasion from mediastinal or hilar nodes survived for over two years after the demonstration of these changes, but in no case was there autopsy confirmation of the reported pulmonary involvement It is perhaps of some interest that all 3 of these patients had an unusually long course, averaging over eight years No definite conclusions can therefore be drawn, but it seems probable that involvement of the lung parenchyma is associated in many cases with rapidly advancing disease

Ziegler concluded that Hodgkin s disease runs a more rapid course in children than in older patients Uddstromer believed the reverse to be true Our own experience is that age alone has little or no influence on the prognosis

That the disease may run an extremely rapid course has been already pointed out For example, a 6 year old girl was noted by her parents to have enlarged lymph nodes in each side of the neck in December, 1933 and one week later developed cough and fever She died of respiratory failure on 10 January 1934, within six weeks of onset

In sharp contrast is the following case

A P, a 10-year old boy, in 1915 developed a painless lump in the left side of the neck It gradually increased in size until November 1917, when it was removed by surgery Histologic examination of the node showed the typical picture of Hodgkin s granuloma (MGH–S17–11–58)

On admission to the hospital on 17 December 1917, physical examination was entirely normal except for the presence of several firm lymph nodes varying from 0 5 to 1 0 cm in diameter, in the anterior triangle of the left side of the neck No lymph nodes were palpable in any other area The red cell, white cell, and differential counts were essentially normal

Between 27 December and 31 May 1918, a total of 6100 mc hr of radium (2 mm of lead and 2 cm of gauze screening) was given to the left side of the neck and the left axilla, although there were no palpable lymph nodes in the latter area The cervical lymph nodes disappeared and the patient was not seen again until 20 December 1924 At that time, he was in excellent condition, and the physical examination was entirely within normal limits

He returned on 22 August 1930, when a 2 cm node was found under the left jaw There were many carious teeth in the lower jaw The node was removed on 6 September The microscopic diagnosis was Hodgkin s granuloma A full suberythema dose of x ray was given at 250 kilovolts over the left side of the neck

Since that time, the patient has remained entirely well When last seen in December 1939 twenty two years after onset, he was free from symptoms and physical examination disclosed no abnormalities

Between the extremes of these two cases lie the majority of cases It is well to bear in mind that it is often difficult to predict the course with any degree of accuracy That such is indeed the fact is well illustrated by a case in which the patient had at onset symptoms of a generalized disease and signs of involvement not only of lymph nodes but of bone, but was alive and at work twelve years later

Rarely sudden death occurs MacCallum describes a case in which the patient leaned forward to drink a cup of tea and died instantly Autopsy showed that the odontoid process of the axis had been completely destroyed by the disease and that the slight effort of motion had dislocated the spinal column so as practically to cut the cord in two One of our patients a boy of fifteen, was eating his luncheon in comparative comfort In the midst of the meal he sighed, laid down his knife and fork and expired Permission for an autopsy was not obtained As Wallhauser points out, the manner and time of death depend on several variable factors chiefly the course — acute or chronic — the organs and situations involved, the degree of anemia secondary infections the quality of the

patient s resistance and the treatment The importance of the last two factors is too frequently overlooked

It is difficult to evaluate the prognostic significance of bone lesions in Hodgkin s disease Many patients in our series so affected died within less than one and a half years of x ray discovery of the lesion and 63 per cent died within less than a year after it A patient with a massive erosion of the sternum however was in seemingly good health and hard at work twelve years after its discovery, and of the patients who died within a year of the demonstration of bone lesions 33 per cent had already had unequivocal signs of Hodgkin s disease elsewhere for three years or more From the available evidence it does not appear that bone lesions materially alter the outlook In this opinion Uehlinger concurs

HODGKIN S SARCOMA

None of our patients with Hodgkin s sarcoma lived for more than three years after onset and nearly 100 per cent died within two years (Table 7) Again one

TABLE 7 *Duration of Disease from Onset to Death in Cases of Hodgkin s Sarcoma*

DURATION *mo*	NO OF CASES
1–6	12
7–12	6
13–24	13
25–36	1
Total	32

sees the sharp contrast between Hodgkin s sarcoma and Hodgkin's granuloma In our experience the former is invariably fatal within a comparatively short period of time whereas the latter usually runs a relatively benign course and in rare cases is actually cured

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PLATE I

Hodgkin's paragranuloma

Hodgkin's granuloma Eosinophils and polymorphonuclear leukocytes

PLATE II

Hodgkin's granuloma Area of Necrosis

Hodgkin's granuloma Fibrosis



HODGKIN'S GRANULOMA MEDIASTINAL INVOLVEMENT BEFORE TREATMENT



THE SAME CASE AFTER TREATMENT



HODGKIN'S GRANULOMA NODULAR LESIONS IN LUNG



HODGKIN'S GRANULOMA SKIN LESIONS

PLATE IV









BONE LESIONS IN HODGKIN'S GRANULOMA

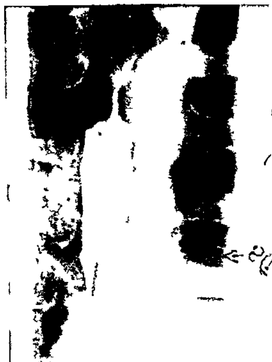
PLATE V



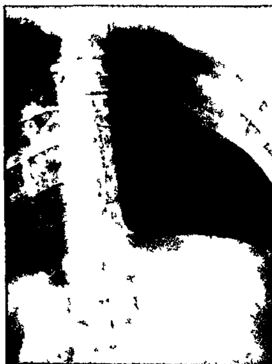
HODGKIN'S GRANULOMA INTESTINAL LESION BEFORE TREATMENT



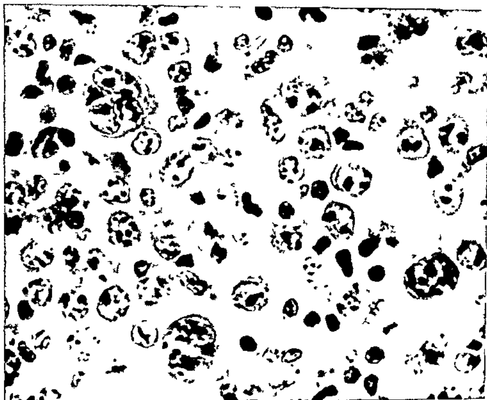
THE SAME CASE AFTER TREATMENT



HODGKIN'S GRANULOMA CISTERNAL PUNCTURE OBSTRUCTION D_8 TO L[illegible]



THE SAME CASE AFTER TREATMENT NO OBSTRUCTION



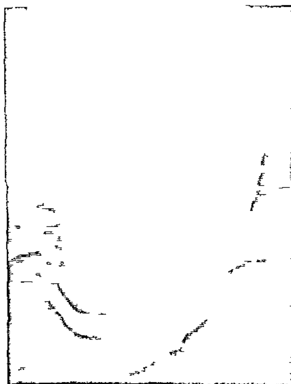
Hodgkin's sarcoma



Hodgkin's sarcoma Reticulum stain



HODGKIN'S SARCOMA SKULL



HODGKIN'S SARCOMA INVOLVING STOMACH

II

Reticulum-Cell Sarcoma

Terminology and Definition

This tumor is known by a confusing number of synonyms such as 'Retothel sarcom' (Roulet), large, round cell sarcoma, lymphosarcoma reticulum cell type, and reticulocytoma As far as we can learn, Ewing in 1913 first suggested that certain tumors might be derived from reticulum cells Many writers have given Roulet the credit of describing this type of tumor, but Ewing definitely has priority since Roulet did not publish his paper until 1930

Many authors still regard reticulum-cell sarcoma as one variety of lymphosarcoma and use the term lymphosarcoma, reticulum cell type However, we believe that reticulum cell sarcoma is a distinct entity from the point of view of histogenesis cell type, pathological and clinical characteristics Some of the more important points of difference between the two types of neoplasms may be mentioned here A number of cases of lymphosarcoma are accompanied by a blood picture of lymphatic leukemia This is never seen in reticulum-cell sarcoma. Reticulum cell sarcoma of bone forms one group of primary bone tumors In our experience on the other hand, true lymphosarcoma never is primary in bone The age incidence of lymphosarcoma shows two main peaks, one in the first, the other in the sixth decade Generalized reticulum-cell sarcoma, arising in lymph nodes, on the contrary, occurs chiefly in the fifth, sixth, and seventh decades, and we have never seen a case under the age of 20, with the exception of those in which the disease was primary in bone The type cell of a lymphosarcoma is a lymphocyte that of reticulum cell sarcoma, a reticulum cell, with each cell morphologically and physiologically entirely distinct and, in the great majority of instances, if the tissue is properly fixed and stained, readily distinguishable from one another.

The term, reticulum cell, in our opinion is unfortunate. However, the name has become so firmly entrenched that the substitution of any other would be unwise The term is unfortunate for several reasons 'Reticulum' is used in two senses one to designate the fibrous supporting tissue of lymphoid tissue, the other to define certain cellular constituents of these same tissues Therefore, the term reticulum per se may mean either one of two separate types of structures and properly speaking the adjective, fibrous or cellular should be added to define its exact meaning However, in common usage, the word reticulum alone is employed to designate the fibrous supporting tissue, and we shall use it in this sense A further objection to the expression reticulum cell is based on the fact that this cell does not produce reticulum but is merely associated with it as are many

other cell types, such as lymphocytes endothelial cells and the various parenchymatous cells of such organs as the liver and the kidneys

The Reticulum Cell

The reticulum cell according to our point of view is identical with the histiocyte clasmatocyte macrophage or large wandering mononuclear cell It is derived from mesenchyma and appears in the embryo at about the same time as the fibroblast It occurs not only in lymphoid tissue but in varying numbers in all tissues In the central nervous system it bears the name of microglia In lymphoid tissue reticulum cells occur in the germinal centers or lie in the interstices of the reticulum fibers and often are applied closely to them

Due to various infections such as diphtheria and poliomyelitis the reticulum cells in the germinal centers of lymph nodes show evidence of marked phagocytosis the cytoplasm being filled with nuclear debris This cell also forms the cellular response to tuberculosis and syphilis in other words those diseases to which the term granuloma commonly is applied Furthermore the giant cells found in the presence of a foreign body are derived from the reticulum cell The reticulum cell then responds to certain bacterial toxins and is also the chief scavenger cell of the tissues phagocyting necrotic cells of all types, and attacking foreign bodies of any nature The littoral cells lining the sinuses of the lymph nodes may become free In such instances the cells are morphologically and physiologically indistinguishable from reticulum cells This is also true of the elements of the so called reticulo-endothelium of other organs and tissues

In summary we believe that the reticulum cell is as much an entity as the fibroblast the smooth muscle cell or the lymphocyte It is not however derived from lymphocytes nor does it develop into them as some authors believe Tumors therefore arising from this cell should be termed reticulum cell sarcomas since they constitute a distinct type in no way related to neoplasms arising from cells of the lymphocytic series namely the true lymphosarcomas

From the considerations given above it is apparent that reticulum cell sarcomas may arise from any organ or tissue in the body

The reticulum cell is considerably larger than a lymphocyte In tissue fixed in Zenker's fluid the nucleus which is from 1½ to 3 times larger than that of a lymphocyte varies in shape from round to oval frequently it is indented or lobulated In the cells of well differentiated tumors the chromatin is finely divided and scattered in the more anaplastic it tends to be coarse, and nucleoli may be prominent The cytoplasm is considerable in amount in relation to the nucleus and varies in its staining reaction from acidophilic to basophilic Evidence of amoeboid activity as indicated by the shape of the cell and its nucleus is present frequently Such marked amoeboid activity is not seen in the lymphocyte or lymphoblast Binucleate forms occur but true tumor giant cells do not The stroma varies in amount from delicate strands of collagen to dense bundles

By appropriate silver stains it may be seen readily that reticulum fibrils not only surround groups of cells but pass in an irregular manner between individual cells with which they are often in intimate contact

This histological picture — the large, irregular nuclei, the scattered chromatin, the abundant and often amoeboid cytoplasm — is hardly that of true lymphosarcoma, in which the cells are uniform, smaller, and of more regular shape, and in which the basophilic cytoplasm is scant and the chromatin gathered in heavy clumps.

Point of Origin and Organ Involvement

From our 28 autopsies on cases of reticulum cell sarcoma, which occurred among a total of 18,668 autopsies at the Boston City Hospital, it would seem that the point of origin of the tumor was most common in the retroperitoneal nodes or in the gastrointestinal tract. Occasionally it arose in the mediastinal or cervical nodes or in the pharynx. Three tumors were primary in the substance of the brain (Table 1).

Table 1. *Reticulum Cell Sarcoma. Apparent Site of Origin (28 Autopsies)*

		NO. OF CASES
Retroperitoneal nodes		9
Gastrointestinal tract		6
Stomach	4	
Colon	1	
Jejunum	1	
Mediastinal nodes		3
Cervical nodes		2
Temporal lobe		3
Bone		2
Tonsil		1
Spleen		1
Iliac nodes		1

Clinical evidence substantiates the frequency with which the tumor originated in the gastrointestinal tract, especially the stomach, but indicates, on the other hand, a frequent origin in the pharynx, especially the tonsil, and in the cervical lymph nodes.

LYMPH NODES

The lymph nodes were involved by tumor in 24 of our 28 autopsied cases. In 1 case the lymph nodes, unfortunately, were not examined, as the presence of tumor was not recognized at the time of autopsy. In 15 instances the tumor was primary in lymph nodes distributed as follows: retroperitoneal, 9 cases, mediastinal, 3 cases, cervical, 2 cases, and iliac, 1 case. The peripheral lymph nodes were found at autopsy to be involved in 10 instances: the cervical nodes in 4, the inguinal nodes in 2, those of the axilla in 2, cases and both the cervical and inguinal nodes in 2 cases.

GASTROINTESTINAL TRACT

The gastrointestinal tract was involved in 13 of the 28 cases. In 4, the condition was clearly primary in the stomach. In each case, the process was extensive, in 1 virtually the entire stomach was involved. In another, the upper part of

the lesser curvature, most of the posterior wall, and part of the greater curvature were implicated In the other 2 also, the lesion was extensive, 1 being situated near the pylorus and the other along the greater curvature The descending colon was primarily involved in 1 case, and secondary nodules varying in size from pinhead to 1 to 2 cm, almost invariably white in color, were found in various parts of the gastrointestinal tract In 3 cases, such nodules were found in the stomach, in 3, the rectum was implicated and in similar fashion, there were nodules in the esophagus and small intestine in 2 cases It is noteworthy that in but 1 case were the lesions ulcerated The clinical implications of this observation are obvious Tumors arising in the gastrointestinal tract are of importance because of their extent and their similarity to carcinoma

LIVER

The liver was involved in 10 cases, in 2 there was both direct extension from a tumor primary in the stomach and metastatic nodules. In the other 8 cases, the lesions were purely metastatic Both the number and size of the metastatic nodules varied greatly Some were but a few millimeters in diameter, while others measured up to 3 centimeters in diameter Their shape was either spherical or irregularly linear, when they followed the distribution of the portal areas The color of the nodules was white The size of the involved livers usually varied from normal to moderately enlarged In only 1 instance was the organ markedly enlarged, weighing 3,790 grams

PANCREAS

The pancreas was involved in 10 cases In 7, there were small metastatic nodules, in 3, the organ had been surrounded and invaded by tumor of the retroperitoneal lymph nodes

SPLEEN

The spleen was involved in 9 cases In 1 the tumor apparently was primary in that organ which weighed 1,300 grams The spleen was grossly involved in the 7 other cases and only microscopically in 1 The affected spleens were markedly increased in size the smallest weighing 660 grams and the largest 1,350 grams The tumor appeared as numerous greyish white nodules or bands of tissue varying in diameter from 1 millimeter up to several centimeters, and stood out against the normal red color of the pulp The capsule was not involved, although tumor nodules could be seen through it

ADRENALS

In 7 cases, tumor tissue was found in the adrenals, most frequently as small nodules in the medulla Rarely the cortex was invaded

BONE

Primary reticulum cell sarcoma of bone is considered separately In our 28 autopsied cases of generalized reticulum cell sarcoma bone was involved in 7 cases In 1 there was direct extension to the hard palate, in another, the tumor

had extended directly from the retroperitoneal lymph nodes to the lumbar vertebrae In 5 others, small metastatic lesions were found chiefly in the vertebrae and sternum Tumors arising in bone are of especial interest, because, though *often extensive, they are more amenable to appropriate treatment* than most malignant tumors of bone

LUNGS

The lungs were affected in 7 cases In 4, the tumors were metastatic, and in 3, there was direct extension from other involved structures In 3 of the metastatic cases, no gross tumor was visible In the fourth, both lungs contained numerous, firm, grey red nodules varying in diameter from 2 to 3 cm In the 3 cases involved by extension, 1 showed no gross tumor In 1, the tumor, primary in the mediastinal nodes, extended into the right lung at the hilus, distal to which the bronchi were dilated and filled with purulent material The left lung was not involved In the third case, the tumor was primary in the stomach and had extended upward through the diaphragm

KIDNEYS

Small metastatic nodules were found in the kidneys in 5 cases, in the sixth case, the organ was invaded from without and also was studded with small metastatic nodules

HEART

The heart was invaded in 6 of our autopsied cases In 2, there was extensive involvement of the pericardium with bloody effusion in 3, there were isolated, white nodules either in the auricle or pericardium In the sixth, the heart weighed 380 grams, and the tumor surrounded the pulmonary veins and arteries and the superior vena cava The neoplasm averaged 5 mm in thickness, and numerous small polypoid growths were seen on the wall of the right auricle and along the course of the left descending coronary artery

BRAIN

The temporal lobe of the brain was the primary site of the disease in 3 of our 28 cases These have been discussed in detail by Yuile and by Kinney and Adams In a fourth, there was extension from the bone of the skull into the substance of the brain Tumors primary in the brain are of especial interest because of the great rarity with which this organ is implicated by any form of lymphoma

TONSIL

In 1 case, the tumor originated in the tonsil

INCIDENCE

In general, reticulum cell sarcoma is a disease of elderly people, though it is found occasionally in the twenties (Table 2) and, as will be discussed later that form which is primary in bone is not uncommon in youth We cannot agree with Sugarbaker and Craver that in 'lymphosarcoma, reticulum cell sarcoma type'

the age distribution is very uniform nor do their own figures seem to support this contention

Sixty four of our 116 cases were men.

TABLE 2 *Reticulum Cell Sarcoma Age at Onset*
(116 Cases)

AGE	NO OF CASES
0–9	0
10–19	0
20–29	13
30–39	6
40–49	25
50–59	29
60–69	28
70–79	13
80–89	2

SYMPTOMATOLOGY

The common initial symptoms (Table 3) reflect the invasive and destructive character of the condition Pain often constant and occasionally extreme is common and is liable to be resistant to the usual forms of irradiation therapy It is most common in the neck or deep in the abdomen It cannot we believe be too strongly emphasized that persistently enlarged nodes in an adult in absence of obvious adjacent infection must be regarded as neoplastic until proved by

TABLE 3 *Reticulum Cell Sarcoma Initial Symptoms*
(116 Cases)

		NO OF CASES
Pain		43
Head and neck	15	
Abdomen	14	
Chest	7	
Legs	[illegible]	
Enlarged lymph nodes		24
Cervical	21	
Inguinal	3	
Sore throat		23
Dysphagia		10
Loss of weight		10
Vomiting		[illegible]
Nasal obstruction		6
Dyspnea		5
Epistaxis		4
Enlarged tonsils		4
Weakness		4
Hoarseness		3
Edema, cough melena deafness sk[illegible] odules		1 each

biopsy to be of benign or infectious nature Enlarged lymph node[illegible] n the cervical region are frequent early in the [illegible] ficial painless lymph[illegible] than in Hodgkin [illegible] The nodes often are painful occasi[illegible] usually firm or even of the stony hard con

sistence usually regarded as characteristic of metastatic carcinoma In sharp contrast to Hodgkin's granuloma, the nodes often are fixed to the underlying tissues, and occasionally the overlying skin is thickened and of a dull, brownish red color The firm consistence of the nodes and their tendency to fixation is of some value in the clinical differentiation of reticulum-cell sarcoma from Hodgkin's disease Long continued sore throat was an initial symptom in over 20 per cent of our cases, and the persistence of this symptom for any great length of time in an elderly patient always should arouse the suspicion of malignant disease, particularly if associated with bleeding, notable enlargement of the tonsil, or other symptoms suggestive of neoplastic disease Dysphagia was found to be an occasional initial complaint It may be caused by pressure from enlarged lymph nodes or much more rarely by an intrinsic lesion of the esophagus itself Loss of weight is frequent, even early in the disease Nasal obstruction, often intermittent and associated with a purulent or more rarely a sanguinous discharge, is an uncommon but important initial symptom as pharyngeal reticulum cell sarcoma is one of the most formidable and distressing forms of the disease These nasal symptoms in elderly people, when not caused by obvious infection must be evaluated very carefully The remaining initial symptoms which have been encountered in our series further attest the malignant and destructive character of the disease

Chills, fever, general malaise, and sweating are conspicuously absent, particularly so in contrast to Hodgkin's granuloma

It has been pointed out already that reticulum cell sarcoma may arise in any organ of the body, and, of course, any organ may be invaded subsequently either directly or by metastatic nodules (Table 4) This is true also in Hodgkin's disease, but from a clinical point of view, there is a very great difference between these conditions, not only in regard to their initial symptomatology but also in respect to the organs involved In reticulum cell sarcoma, neither the mediastinum nor the lungs are involved nearly so commonly as in Hodgkin's granuloma or sarcoma, nor are the liver and spleen, and these latter organs, even when involved, are not apt to reach the massive size often seen in Hodgkin's disease On the other hand, clinical evidence of secondary bone lesions is relatively uncommon in reticulum cell sarcoma (16 per cent) as compared to Hodgkin's sarcoma (50 per cent), though rarely one sees massive bone destruction apparently secondary to a focus elsewhere and similar to the massive primary reticulum-cell sarcoma of bone to be described later Involvement of the pharynx is common in reticulum-cell sarcoma (64 per cent), rare in Hodgkin's sarcoma (15 per cent), and exceedingly rare in Hodgkin's granuloma Of the pharyngeal tumors, those of the tonsils are by far the most frequent

GASTROINTESTINAL TRACT

Clinical evidence of the involvement of the gastrointestinal tract is seen in approximately 20 per cent of the cases The lesion usually is single and is most common in the stomach, where it may give rise to symptoms indistinguishable from those of carcinoma, namely, epigastric pain, anorexia, vomiting, hematemesis, and often marked and rapid loss of weight Unfortunately such lesions often are silent

TABLE 4 *Reticulum-Cell Sarcoma Organs Involved Clinically in 102 Cases Followed to Date or to Death*

		NO OF CASES
Superficial lymph nodes		71
Pharynx		33
Tonsil	18	
Nasopharynx	7	
Palate	5	
Posterior pharynx	3	
Multiple	6	
Gastrointestinal tract		23
Stomach	10	
Esophagus	3	
Ileum	3	
Cecum	3	
Rectum	3	
Sigmoid	1	
Multiple	1	
Mediastinal nodes		15
Spleen		15
Bone (secondarily involved)		15
Skin		13
Liver		10
Nervous system		10
Lungs		7
Breast		5
Genitourinary tract		2
Thyroid		1

Gross lesions elsewhere in the gastrointestinal tract similarly give rise to pain and occasionally are associated with a palpable mass Rarely, there may be an isolated solitary tumor amenable to surgical removal with some hope of permanent cure Perforation occurs rarely, but the tumor has a strong tendency to infiltrate neighboring organs and extend to local lymph nodes

NERVES

The implication of peripheral or cranial nerves is not uncommon giving rise to palsies of various sorts, often amenable to appropriate radiation.

BLOOD

A slight degree of normochromic or hypochromic anemia is seen in approximately 35 per cent of the cases Severe anemia is very rare In only 6 of our cases did the red count fall below 3 000 000, and in but 2 was a level less than 2 000 000 reached In each of these latter cases, the disease was unusually widespread, and in each, anorexia and loss of weight were extreme The comparative absence of marked anemia in this disease is noteworthy when contrasted with Hodgkin's granuloma

The white count does not deviate greatly from the normal Very rarely there is a moderate, 15,000 to 20 000, leukocytosis Leukopenia we have never encountered In some cases, there is a moderate and in a rare case, a marked increase in the per cent of polymorphonuclears Again the sharp contrast between this disease and Hodgkin's granuloma is striking

As has been stated already we have never seen the development of lymphatic leukemia referred to by Sugarbaker and Craver as a not infrequent termination of *reticulum cell lymphosarcoma* Very rarely does leukemia the type cell of which is a reticulum cell develop When it does take place however death is not far off One of our patients with reticulum cell sarcoma apparently primary in the breast developed an acute leukemia but the cells were too immature to identify even after the most painstaking efforts Death ensued shortly

Just as there are cases of lymphatic leukemia without any evidence of lymphosarcoma so there may be reticulum cell leukemia with no evidence of reticulum cell sarcoma This seeming paradox in no way precludes the association of a lymph node tumor with its corresponding leukemia However it is true that there is no characteristic blood picture of reticulum cell sarcoma

SYMPTOMS DEVELOPING IN COURSE OF DISEASE

Once the condition has made itself manifest further symptoms are fast in appearing and these once more indicate the destructive nature of the disease (Table 5) It is to be noted in particular that loss of weight and pain are common and often extreme We have seen 1 patient die apparently from excessive continuous and irremediable pain Sore throat dysphagia hemoptysis hematuria melena and nasal obstruction are seen more commonly during the course of the disease than in any other form of lymphoma

TABLE 5 *Reticulum Cell Sarcoma Symptoms Developing during Course (98 Cases)*

	NO OF CASES
Loss of weight	64
Pain	54
Anorexia	36
Dyspnea	21
Cough	15
Edema	14
Sore throat	14
Fever	13
Vomiting	12
Melena	10
Dysphagia	8
Effusion	7
Nausea	7
Nasal obstruction	7
Diarrhea	6
Hemoptysis	6
Jaundice	6
Hoarseness	6
Hematuria	5
Enophthalmos	5
Hematemesis	5
Ascites	3
Constipation	3
Chills	2

On the other hand pronounced fever unless due to associated sepsis is rare and the *itching and marked* tachycardia so common even early in Hodgkin's

granuloma is almost never encountered The so-called Pel–Ebstein fever does not occur in this condition

The usual course of the disease is relentlessly onward The spontaneous remissions, occasionally seen in Hodgkin's granuloma, do not, in our experience, occur

Diagnosis

It is doubtful whether a clinical diagnosis of reticulum cell sarcoma can be made with any degree of certainty As with other forms of malignant lymphoma, a biopsy is necessary and it is imperative that the tissue be well fixed and well stained It is our opinion, and it was that of Ewing that improperly fixed thick poorly stained sections are the cause of much of the confusion arising in this already complicated field of lymphomas

When superficial lymph nodes are the sole objective evidence of the disease, *reticulum-cell sarcoma* may be indistinguishable from *Hodgkin's* granuloma Hodgkin s sarcoma, carcinoma tuberculosis or even sarcoid The disease may be suspected, however, when the involved lymph nodes are hard somewhat fixed to the underlying or overlying tissues and painful As has been said the overlying skin occasionally is reddened and thickened The absence of fever, the presence of a normal white-cell count and differential cell count are of some importance in the differential diagnosis

When the mediastinal nodes are involved primarily, an exact diagnosis can be made only by biopsy of a *superficial metastatic* node *In the presence of such* symptoms as loss of weight anorexia and dyspnea, it is patent that a careful physical and x ray examination is in order, and it is important to recall that the process may be entirely internal and that, therefore, the diagnosis may be difficult or indeed for a time impossible

In the pharynx, the disease may be suspected in the presence of a bulky, obstructive tumor that is often painful in a comparatively young person, 25 to 50 years old A similar tumor in an older person cannot be differentiated clinically from carcinoma

Similar principles can be applied with some measure of success to reticulum-cell sarcoma *of the gastrointestinal tract though it should be remembered that* carcinoma of the stomach is not rare in comparatively young persons

Illustrative Cases

The following cases illustrate some of the more important types of the disease

Case 1 M C (B C H 756097) This 44 year-old man was admitted to the *hospital* on 14 March 1935 In January 1934 he began to have severe, intermittent, frontal headaches particularly on the right side Six months later he became *increasingly deaf in the right* ear, and at the same time he noticed enlarged hard non tender lymph nodes high in the right neck *One of these was* removed and showed the typical picture of *reticulum-cell sarcoma (S34–2666)* During the succeeding two months 2 000 r of x ray were given to the right side of the neck with much relief of symptoms In September 1934 the patient complained of nasal obstruction, and on physical examination there was found a large

polypoid tumor which nearly filled the nasopharynx Biopsy of this mass again showed reticulum cell sarcoma The headaches and deafness recurred and increased in severity, and enlarged nodes were noted for the first time in the left side of the neck in both anterior and posterior triangles During the next two months, he received a total of 3 400 r of x ray divided equally between the two sides of the neck He left the hospital against advice and at another institution received an additional 4 000 r Following this treatment all the enlarged lymph nodes disappeared but the patient returned to our clinic and was admitted to the medical ward Physical examination in March 1935, showed a few small very hard, fixed lymph nodes in either side of the neck There was no other lymphadenopathy The nasopharyngeal tumor was still present though much smaller The patient was completely blind in the left eye There was marked ptosis of the left lid and paralysis of the left abducens nerve X ray films showed some destruction of the inferior orbital plate on the left side The remainder of the physical examination was essentially normal The patient complained of severe constant left sided headache Further high voltage x ray therapy brought no relief Six weeks after this hospital admission there developed a complete left facial paral

lost weight

Throughout

At no time

was there an elevated white blood cell count though there was a constant marked increase in the per cent of polymorphonuclears No fever was present at any time The basal metabolic rate at all times was normal

Both deafness and various ocular disturbances such as blindness and enophthalmos are not unusual in reticulum cell sarcoma The eye signs, especially enophthalmos may respond quite dramatically to appropriate x ray therapy

Case 2 E D (P 7192) This 23 year-old man first noted nasal obstruction and bilateral painless enlargement of the cervical lymph nodes in January 1930 In October 1930, he was admitted to another hospital for increasing nasal obstruction and a unilateral, purulent, nasal discharge At that time a tonsillectomy was performed, and a diagnosis of lymphoblastoma' was made An unknown

nasal obstruction and severe pain in the left ear On entry, physical examination revealed no abnormalities except for a large polypoid mass nearly filling the nasopharynx A biopsy of this tumor showed it to be reticulum cell sarcoma His red blood-cell count was 3 920 000 hemoglobin 80 per cent The white blood cell count was 9 300, the differential was normal During the next two months, 4 200 r of x ray were directed to the tumor but there was no favorable response The patient complained of increasing anorexia, deafness and earache He lost 30 pounds of weight The patient gradually failed the earache became extreme and could be controlled only by large doses of morphine Death occurred from bronchopneumonia early in January 1934, four years from onset

Autopsy (PA34-16) showed marked cachexia and bilateral bronchopneumonia The reticulum cell sarcoma was confined to the nasopharynx, the left tonsillar fossa and the cervical lymph nodes

Case 3 F J (S D 76642) This 48 year-old man was sent in to the hospital

with a diagnosis of diphtheria For ten days prior to admission he had suffered from an increasingly severe sore throat For four days he had had pain in the right ear His past history was irrevelant On entry physical examination was essentially negative except that a yellowish gray membrane covered the uvula and the right side of the soft and hard palate portions of which were deeply ulcerated The peripheral blood picture was essentially normal The Wassermann reaction was positive While in the hospital he ran a moderate degree of fever A tentative diagnosis of syphilis was made and the patient was treated with sulpharsphenamine and potassium iodide Despite these therapeutic measures however the ulcerations continued to spread and during the ninth hospital week, the major part of the palate sloughed away leaving a large perforation into the nasal cavity During the twelfth hospital week the patient's pulse rose to 130 and the respiration to 35 He frequently spit up large amounts of very foul sanguinopurulent material The patient grew progressively weaker and the red blood cell count dropped to 2,500 000 The white blood-cell count and differential remained essentially normal He died on 4 May 1927

Autopsy (A27–168) showed very extensive reticulum-cell sarcoma of the hard and soft palate the tonsils and posterior pharyngeal wall with extension to the maxilla, nasal septum base of the tongue and larynx There were in addition metastases to the lungs liver spleen and heart and accumulations of sterile pus in the peritoneal and pericardial cavities

Each of these cases illustrates the invasive destructive and often comparatively localized nature of the condition as well as the relatively poor response to irradiation

A more unusual type of this disease is illustrated by the following case

CASE 4 J D 840386 This 50 year-old Italian was admitted to the hospital on 3 November 1936 His past history was irrelevant For a period of two weeks prior to admission he had complained of increasing drowsiness and severe headaches On several occasions he had vomited Physical examination showed an exceedingly drowsy weak somewhat disoriented man The pupils were normal The tongue deviated to the left There was marked weakness of the left arm and leg and all tendon reflexes on the left side were increased There was a positive Babinski reaction on the left Otherwise the physical examination showed no noteworthy abnormalities A lumbar puncture showed an initial pressure of 240 mm and a pressure of 140 mm after the withdrawal of 10 cc of clear pale amber fluid The spinal fluid showed 7 lymphocytes and 9 red cells per cu mm The Pandy test for globulin was 2+ The total protein of the spinal fluid was 120 mgm per 100 cu mm The Wassermann reaction was negative The gold curve was 0112222110 The patient remained in the hospital for twelve days gradually growing weaker The neurological signs remained essentially the same Bronchopneumonia developed at the right base and on the twelfth hospital day he sank into a deep coma and died eight hours later

Autopsy (A36–595) showed an extreme degree of cerebral edema and a moderately large tumor mass in the central portion of the right hemisphere with invasion of the claustrum external capsule and lateral edge of the right internal capsule

That the outlook for patients with reticulum-cell sarcoma is not always so gloomy as would appear from those just cited is attested by the following

CASE 5 M N (H H 36–113) This 54 year old Armenian man was seen first in February 1936 A month before, he had noted enlarged nodes in each side of the neck and axilla His past history was irrelevant, and there had been no loss of weight Physical examination showed several, olive sized, hard, non tender lymph nodes in each axilla and in either side of the neck under the sternomastoid muscle Otherwise the physical examination was essentially normal The peripheral blood showed a slight degree of secondary anemia, otherwise no abnor

until April 1937, when he complained of epigastric distress and some difficulty in swallowing solid food

third of the esophagus

symptoms entirely disap

geal lesion Except for minor episodes of lymphadenopathy, which responded well to irradiation, the patient was well when last seen (December 1942), seven years from onset

CASE 6 G A (P 9322). This 23 year old man was seen first in May 1935 In November 1934, he developed severe, constant pain in the right, lower quadrant There was no vomiting, diarrhea, constipation, or melena He was examined in an outside hospital at that time, and a mass was felt in the region of the appendix A transverse ileocolostomy was performed On admission in May 1935, physical examination revealed a very tender orange-sized mass in the right lower quadrant Otherwise, the physical examination was normal There was no loss of weight, and the peripheral blood picture was normal The abdomen was opened, and a mass was found involving the cecum and adjacent mesenteric lymph nodes A right colectomy was performed All involved tissue was removed and postoperatively 1,200 r of x ray was given to the anterior and 1,200 r to the posterior abdomen Convalescence was uneventful and the patient is alive and well to date (May 1946), eleven years after operation

This single case, sent to the hospital where a diagnosis of inoperable carcinoma of the intestine was made attests the value of courageous radical surgery in a small number of cases

TREATMENT

The treatment of choice in those forms of reticulum cell sarcoma that are not amenable to surgical intervention (and it must be confessed that very few are) is heavy irradiation with high voltage x ray, though it must be said that this form of therapy is not always attended by any notable degree of success Often, however, the results of x ray are at least temporarily gratifying as in the case of L T (P 1391), whose cervical nodes, though very extensive, disappeared completely in a short time and did not reappear Two years later, the patient noted increasing constipation, and a barium enema showed an obstructing tumor at the rectosigmoid junction He refused all treatment, however, and died six months later It is possible that irradiation of the gastrointestinal lesion would have prolonged his life still further For those cases in which the disease appears to be more or less generalized, our experience would lead us to believe that heavy doses of x ray are indicated We are inclined to favor the x ray therapy program out-

[illegible] Sugarbaker and Craver and to advocate as they do a total dosage of 2 000 to 3 000 r to each area involved this amount to be given over an appropriate period of time If the process is sharply limited yet not amenable to radical intervention as for example in the nasopharynx we should advocate such dosages of x ray as are employed in carcinoma namely from 5 000 to 8 000 r over an appropriate period of time Further x ray therapy should be withheld until new signs or symptoms require treatment It is our firm belief that the roentgenologist and clinician should follow the patient together and that decisions about treatment should be reached in consultation It is hardly necessary to point out that the treatment of each case must be individualized If the process is apparently sharply confined and no distant metastases are apparent radical surgery seems clearly to be indicated It should be remembered however that like other sarcomas the pathological process often extends beyond the limits that are obviously diseased and therefore excision should be wide

Prognosis

In general the prognosis of reticulum cell sarcoma is poor (Table 6)

Neither *age nor sex* appear to be of any particular prognostic import In general, those patients whose initial symptom is merely painless lymphadenopathy have a relatively good prognosis Of the 22 cases in whom the disease first manifested itself in this manner 55 per cent survived the three year period and the average duration of life in this group was 3 6 years 5 survived over six years On

TABLE 6 *Reticulum Cell Sarcoma Duration from Onset to Death (88 Cases)*

YEARS	NO OF CASES	PER CENT
0 0– 1 0	46	52
1 1– 5 0	36	41
5 1 10 0	5	6
Over 10	1	1
Duration from Onset to Date (12 Cases)		
0 0– 1 0	3	20
1 1– 5 0	5	50
5 1–10 0	2	20
Over 10	1	10
Died of Unrelated Causes		
	3	
Lost		
	13	

the other hand when the disease begins with pain or with symptoms such as dyspnea melena or hematemesis indicating involvement of internal organs the outlook is correspondingly poor Seventy five per cent of the patients who lived more than three years had painless enlargement of superficial lymph nodes as the first obvious sign of the condition while of those patients who lived six months or less nearly 90 per cent had initially pain or some symptom indicating visceral involvement Neither splen[illegible] nor hepatomegaly appear *to be of* prognostic importance but involveme[illegible] diastinal nodes the lung or the

gastrointestinal tract is of ill omen Fourteen of our 18 cases that lived less than six months from onset had involvement of either the lung mediastinal lymph nodes or gastrointestinal tract and all of those patients with mediastinal or gastrointestinal tract involvement died within less than one year of onset except one in whom the disease was discovered comparatively early so that radical surgical intervention could be carried out with apparent success It should be remembered that as in other forms of malignant lymphoma sudden death may occur usually from rupture of a hollow viscus

PRIMARY IN BONE

Incidence and Pathology

In 1939 reticulum cell sarcoma of bone was added to the list of primary bone tumors in the revised classification of the Registry of Bone Sarcoma of the American College of Surgeons (Ewing 1939) Thirteen of these neoplasms previously had been classified as Ewing s sarcoma Hodgkin s disease lymphosarcoma osteogenic sarcoma or as an inflammatory process In view of the fact that primary reticulum cell sarcoma of bone has been readily diagnosed only recently and because the prognosis is comparatively good if the disease is promptly and radically treated it seems appropriate to devote a special section to its consideration The clinical and pathological aspects of this tumor were reported in some detail by us in 1939

From the Registry of Bone Sarcoma we have collected 13 cases and from our own material we have added 12 more Of the 25 cases 13 were men and 12 were women

The age distribution of primary reticulum cell sarcoma of bone differs materially from that of the generalized or soft tissue form of the disease which as has been pointed out already is primarily found in middle and old age 85 per cent of the cases occurring after the age of 40 and none of our series being under 20 years of age In sharp contrast as will be noted in Table 1 64 per cent of

Table 1 *Primary Reticulum-Cell Sarcoma of Bone Age at Onset (25 Cases)*

AGE	NO OF CASES
0- 9	0
10–19	7
20–29	3
30–39	6
40–49	3
50–59	3
60–69	3

the primary reticulum-cell sarcomas of bone occurred under the age of 40 and 28 per cent below the age of 20 In view of the highly malignant nature of most primary bone tumors in the early decades these facts should be clearly recognized

In the generalized form of the disease the rather uncommon metastatic bone

lesions occur most often in the vertebrae and skull On the contrary, primary reticulum-cell sarcoma of bone is found most frequently in the long bones (Table 2)

TABLE 2 *Primary Reticulum Cell Sarcoma of Bone Bone Involved (25 Cases)*

BONE	NO OF CASES
Femur	5
Clavicle	5
Tibia	5
Humerus	4
Vertebra	3
Scapula	1
Mandible	1
Maxilla	1

The type cell is identical with that of reticulum cell sarcoma of lymph nodes and other tissues

A fairly common feature of these tumors is the growth of cells in the walls of small veins In such vessels the endothelium is lifted and the lumen encroached upon and distorted by tumor cells in the intima We have not seen similar involvement of the arteries or arterioles Necrosis of the infarct type is often a prominent feature Complete destruction and obliteration of the normal constituents of the marrow is found constantly Osteolysis also is often a prominent feature The tumor cells do not form new bone, although new bone formation by the stroma does occur

Metastases fortunately are late and are seen chiefly in the neighboring lymph nodes In only 1 instance (1951) have we seen [illegible]
tases In another case [illegible]
plete resection of a [illegible]

In gross appearance, the tumor varies considerably In early cases, the medullary cavity is invaded by pinkish gray granular, neoplastic tissue In more advanced cases, there is more obvious bone destruction, and the soft tissue involvement already referred to is obvious The tumor in these instances is usually firm, smooth, and glistening more rarely it is soft and friable The color is described variously as pale white pinkish gray, and gray white Areas of necrosis are frequent and may merge into large cavities resembling *osteomyelitis*

SYMPTOMATOLOGY

Clinically the onset is similar to that of many other primary bone [illegible] ors namely with pain not relieved by rest [illegible]

[illegible] complaint In 10 [illegible] obvious tender swelling of the affected part It is to be particularly noted that the general health of the patient when first seen, was good in all but 2 cases (547, 1663) In these 2 there had been great loss of weight and strength yet both cases are alive and well ten years later In 3 cases the

spine was involved One of these has been described in detail by Edwards Another was operated on and the tumor completely removed Unfortunately, the patient died of respiratory failure shortly thereafter The third had an in complete resection and died at home of an unknown cause In no case was fever noted In no instance were there notable abnormalities in the peripheral blood picture The few blood calcium and phosphatase determinations which have been done, were within normal limits but the number of determinations are too few to be of significance A history of injury preceded the initial symptoms in 6 of the 25 cases, but there is no good evidence that trauma actually is of etiological importance It seems more probable that a minor injury brought on symptoms in an already diseased bone, or that a previous injury was recollected by the patient, when symptoms of major importance had supervened Perhaps the most important clinical feature is that an extensive, painful destructive process most often in a long bone, is found in a patient of any age, whose general condition usually is good In no other bone sarcoma is the contrast between the comparative well-being of the patient and the extent of the lesion so marked With no other bone tumor may the lesion be so extensive and at the same time be so amenable to appropriate treatment

Often the disease had existed so far as one could tell by the symptomatology, for many months before the services of a physician were sought In 7 cases, symptoms had been present for a year or more before treatment, yet 5 of these patients are alive and apparently well from three to sixteen years later This very fact attests the comparatively benign nature of what appears roentgenographically, clinically, and histologically to be a highly malignant tumor The importance of the recognition of this fact in relation to therapeusis is obvious

Diagnosis

We ought however, to emphasize the necessity of early diagnosis and treatment, for by these means only can one expect to obtain the best results In 1 instance, the signs and symptoms definitely pointing to a tumor of the femur had been present for a year and four months before amputation, and the condition had been diagnosed variously as tuberculosis and arthritis At the time of operation the tumor had reached massive size and inguinal lymphadenopathy was present The patient died three months later It is possible that had an accurate diagnosis been made by biopsy at an earlier date, the results would have been better In the presence of a malignant bone tumor, it does not pay to temporize

The x ray appearance is by no means diagnostic The disease is seen most frequently in the ends of the long bones and extends from the metaphysis to the diaphysis In general x ray examination shows chiefly bone destruction and to a much less degree bone formation Occasionally, pathological fracture is seen as it may be in the metastatic forms of reticulum cell sarcoma In early cases, there may be only mottled bone destruction in the medulla In 1 early case, very fine hairlike striations extended from the irregularly thickened cortex and periosteum into the adjacent soft tissue, giving rise to a picture not inconsistent with osteogenic sarcoma There is often fragmentation of the cortex and a widening of the

shaft, as if from an expansion tumor pressing from within outward Periosteal thickening may be seen both early and late in the disease, as it may in the metastatic lesions secondary to the generalized form of reticulum cell sarcoma Invasion of the surrounding muscle is not uncommon In 1 case, this invasion was so extensive that for some time the tumor was thought to have originated in the soft parts rather than in the bone

Differential Diagnosis

Reticulum cell sarcoma of bone must be distinguished from the following conditions with which it has been confused in the past

HODGKIN'S DISEASE

The granulomatous form of this condition with sclerosis, necrosis, eosinophils, and Reed–Sternberg cells should present no diagnostic difficulty The sarcomatous form, in which the majority of the cells are of the mononuclear type, may simulate closely anaplastic reticulum cell sarcoma, but the presence of occasional typical Reed–Sternberg cells should serve as a differential point. Primary Hodgkin's disease of the bone we believe to be very rare

LYMPHOSARCOMA

The type cell with its round nucleus, scanty cytoplasm, and spherical shape should offer no difficulty In our experience, true lymphosarcoma of the bone is extremely uncommon

EWING'S SARCOMA

Reticulum cell sarcomas most frequently have been diagnosed erroneously as Ewing's tumor In the latter, the uniform appearance of the cells and of their nuclei, their arrangement in strands and cords and the distribution of the reticulum are diagnostic features In Ewing's sarcoma, the reticulum surrounds groups of cells, while in reticulum-cell sarcoma, not only does the reticulum surround groups but also runs between individual cells

OSTEOGENIC SARCOMA

Some of the reticulum cell sarcomas have been diagnosed as atypical osteogenic tumors The lack of any tumor bone or tumor-cartilage formation, the absence of osteoid tissue, and the morphology of the tumor cells should exclude this diagnosis

INFLAMMATION

The diagnosis of inflammation in the past has been made erroneously on several reticulum cell sarcomas The presence of large mononuclear cells and lymphocytes with, in addition necrosis has proved misleading In 1 of our own cases, the infarct type of necrosis and the marked cellular infiltration of the vessel walls lead to an incorrect diagnosis of syphilis Even on a biopsy specimen, this error may be made unless the examination is sufficiently complete and extensive to include visible tumor cells In one case, the massive lesion was so

necrotic that literally scores of sections had to be cut before a definite diagnosis could be made

Treatment and Prognosis

It is impossible at present to conclude exactly what the best form of treatment is Amputation followed by irradiation to the adjacent lymph nodes however appears to give the best results In one instance excision seemed adequate but we believe that amputation should be done whenever possible In addition prophylactic radiation is advisable A biopsy of the lesion may be done safely prior to amputation but it should be emphasized that only by careful microscopical study of a properly fixed and stained section can the correct diagnosis be made

It should be emphasized again that primary reticulum cell sarcoma of bone is an easily recognizable entity occurring at any age presenting rather variable x ray features and often mistaken for other bone diseases both neoplastic and inflammatory If recognized early and attacked vigorously the prognosis may be good in spite of the apparent malignant nature of the tumor

Five of the cases studied received radiation only The results were not encouraging

Three additional cases had initial radiation with complete disappearance of both signs and symptoms of the tumor but in each instance the tumor recurred locally within 6 months Amputation was then done and all 3 patients are alive and apparently free from disease from 11 to 16 years from onset These facts point at the same time to the comparative inefficiency of radiation alone and the value of amputation

Eleven cases had amputation or excision only There were 5 deaths One patient died somewhat over a year after a mid thigh amputation for an extensive lesion of the femur A hip joint amputation would have been preferable One patient died 12 years from onset of an unknown cause the case having been lost sight of One patient died shortly after an attempted removal of all diseased tissue invading the maxilla and antrum Two patients died shortly after the attempted removal of a comparatively localized tumor of the spine The remainder of the cases are alive and apparently well

In 6 cases amputation was followed by x ray therapy One patient so treated died with pulmonary and lymph node metastases after the amputation of a massive tumor of the femur which had been present already for over a year and from which the inguinal lymph nodes had become involved before operation The remainder of the patients in this category are alive and well

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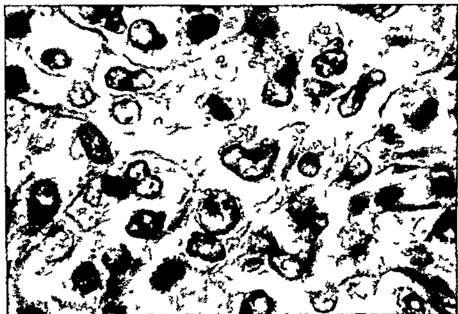
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PLATE VIII

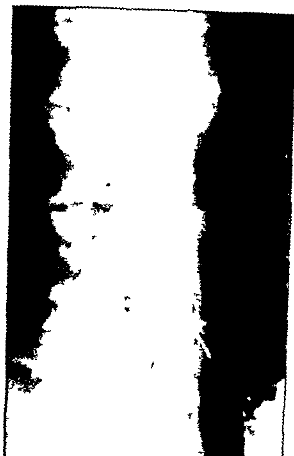


Reticulum cell sarcoma

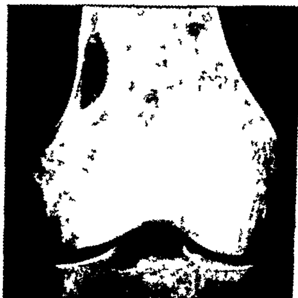
Reticulum cell sarcoma Reticulum stain



Primary reticulum cell sarcoma of bone



Reticulum cell sarcoma of esophagus



Primary reticulum cell sarcoma of femur



Primary reticulum cell sarcoma of mandible

III

Lymphocytoma and Lymphoblastoma

LYMPHOCYTOMAS and lymphoblastomas in contrast to Hodgkin's disease reticulum-cell sarcoma and plasmocytoma have their point of origin almost exclusively in the lymph nodes and in aggregates of lymphoid tissue such as the tonsils The true nature of these neoplasticlike changes of the lymph nodes is obscure This also holds true of the blood dyscrasia lymphatic leukemia which is often associated with them Some workers consider these diseases true neoplasms others consider them abnormal reactions to a variety of causes many of which are unknown (Naegeli lit)

We ourselves feel that the true tumor of the lymphocyte is the lymphosarcoma and are in agreement with those who are doubtful about the neoplastic character of lymphocytomas lymphoblastomas and leukemia In employing such a designation as lymphocytoma and lymphoblastoma we fully realize that it implies a neoplastic process but the names are so widely used in the literature that it would seem unwise to introduce a new term into a field already complicated by an extraordinary complexity of nomenclature

PATHOLOGY

Grossly the affected node or nodes are enlarged and soft to moderately firm in consistence On section the color of the cut surface varies from whitish to gray The outlines of the nodes as a rule are preserved. They do not become fused together nor do they become fixed to adjacent structures

LYMPHOCYTOMA

Microscopic examination shows usually complete loss of structure the germinal follicles being replaced by a massive infiltration of lymphocytes The peripheral sinuses are often compressed and there may be some infiltration of the capsule The type cell is an adult lymphocyte similar in every way to the normal adult lymphocyte Multinucleated cells and giant cells do not occur Mitotic figures as a rule are not numerous Necrosis which is so common in other types of lymphoma is not seen in lymphocytomas nor is fibrosis The reticulum is not increased On the contrary it often appears decreased due to separation of the pre-existing fibers by the dense infiltration of cells

Lymphocytomas may be associated with a chronic lymphatic leukemia or may be the peripheral manifestation of a lymphosarcoma It is impossible to determine from the histological picture whether either or both these other conditions are present In certain cases in which neither lymphatic leukemia nor lympho

sarcoma develops, the existent lymphocytoma seems compatible with a comparatively long life.

Lymphoblastoma

The type cell is a lymphoblast This is a round cell two or three times the size of an adult lymphocyte The cytoplasm is scanty and is basophilic The nucleus is round or somewhat irregular in shape and the chromatin is less dense and more scattered than in the lymphocyte Nucleoli are not prominent as a rule The normal structure of the node is replaced by an infiltration of these cells Scattered stem cells are often found among the lymphoblasts, and sometimes a moderate number of adult lymphocytes are present Mitotic figures are frequently numerous Multinucleated forms and giant cells do not occur. The reticulum is not increased

Lymphoblastomas may have an associated leukemia, in which case it is acute lymphatic in type, or they may represent the metastases from a lymphosarcoma

As is true of the lymphocytomas, it is not possible from the histological picture alone to determine the presence or absence of leukemia, nor is it possible to make a diagnosis of lymphosarcoma

When leukemia is present, there is generalized involvement of the lymph nodes and infiltration of the various organs such as the spleen, liver, kidneys, and bone marrow

While lymphocytomas and lymphoblastomas are frequently seen in biopsy specimens from patients with no evidence of leukemia, this is not true of the autopsy findings on such patients By the time a case of lymphocytoma dies, provided the cause of death is related to the disease of the lymph nodes, the patient has developed either a leukemic blood picture or, if not, his organs nevertheless usually show a leukemic infiltration

Table 1 *Lymphocytoma and Lymphoblastoma* (303 *Cases*) *

AGE AT ONSET yr	NO OF CASES
0– 9	53
10–19	28
20–29	28
30–39	1
40–49	1
50–59	53
60–69	102
70–79	37

* Including 263 showing manifest leukemia

Diagnosis

If a patient presents himself with localized or generalized lymphadenopathy and has, at the same time, the blood picture of lymphatic leukemia, a biopsy is rarely done, for it is unnecessary The manifest leukemias we do not intend to discuss On the other hand, if a patient has similar lymphadenopathy but an essentially normal blood picture, a biopsy is necessary for a correct diagnosis

One cannot otherwise distinguish such enlarged lymph nodes from those involved by Hodgkin's disease, giant follicle lymphoma, reticulum cell sarcoma, or tuberculosis, nor, for that matter, from many other conditions

We should like to emphasize once more that notable lymphadenopathy in an adult particularly if painless is rarely due to a simple inflammatory process unless there is a definite and easily recognizable infection in the immediate neighborhood In children such dogmatism is less justifiable

The age incidence is given in Table 1

The initial symptom is most frequently enlarged nodes in the neck and less frequently nodes in the inguinal region Rarely, there is axillary lymphadenopathy and very rarely, systemic symptoms such as fatigue

The course of the disease is extremely variable Rarely, it seems to be a relatively benign condition Three of our patients are still alive and seemingly well ten years and more after the onset Nearly 50 per cent of the cases die of totally unrelated causes, such as heart failure, cerebral hemorrhage, or intercurrent infections The majority of this category fall into the older age group

The following case history illustrates this course of events

M M (H 39–1262) was a 12 year old girl who entered the hospital in October 1939 In August of the same year, she had noted enlarged lymph nodes in each side of the neck There were no systemic symptoms

On admission to the hospital, physical examination showed that there were many almond sized lymph nodes of rubbery consistence in each side of the neck, and a few similar ones in the left groin They were not tender nor was the skin over them reddened Otherwise, physical examination revealed no abnormalities The red-cell white cell and differential counts were all within normal limits Biopsy of a cervical lymph node showed lymphocytoma A rather small amount of x ray therapy was directed to the neck and groin The lymph nodes promptly regressed but returned four months later, at which time the patient showed the typical blood picture of aleukemic lymphatic leukemia The spleen had become palpable on inspiration In spite of further x ray therapy generalized lymphadenopathy developed the red cell count fell to 1 7 million and the patient died eight months from apparent onset There was no autopsy

It should be apparent from this case that an apparently simple lymphocytoma even without any systemic symptoms, cannot be regarded except in rare instances, as benign

Owing to a number of factors, including perhaps the occasional benignancy of the condition we lose sight of a far greater number of these patients than of those cases with Hodgkin s disease, lymphosarcoma and the like By and large, we lose contact with patients who remain comparatively well or those who later develop some condition unrelated, as far as they are aware, to their first illness

Treatment

The treatment of the condition will of course vary with the course of events and the underlying condition of which the lymphocytoma or lymphoblastoma may be but the outward and visible sign If the disease is sharply limited, local

x ray therapy is all that is needed, and it is, perhaps, a matter of personal opinion whether comparatively small palliative doses should be given or whether one should give all the traffic will bear as with certain types of carcinoma We find little evidence to support the latter thesis If there be generalized lymphadenopathy, with or without the subsequent development of lymphatic leukemia we believe that moderate doses of x ray, together with such adjuvants as transfusions as may seem wise are all that are necessary If the lymphocytoma or lymphoblastoma is the peripheral expression of a true lymphosarcoma, the treatment is of the latter disease

Prognosis

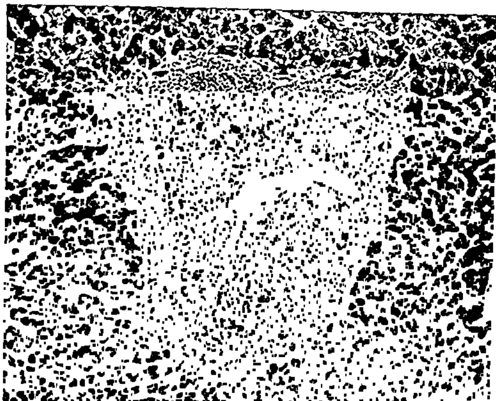
The prognosis is so varied and depends so much on the nature of the underlying condition that actual figures mean little Suffice it to say that if leukemia or lymphosarcoma develops the outlook is extremely grave but that if neither of these complications occur the prognosis is fairly good It must be said, however that these latter cases are few and it should be recognized that the younger patients are prone to develop leukemia and die shortly while the older *patients may die of intercurrent disease In short the outlook is far from bright*

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LYMPHOCYTOMA

LYMPHOBLASTOMA



Lymphatic leukemia. Infiltration of the liver.



Lymphocytoma of lymph node.

IV

Lymphosarcoma

LYMPHOSARCOMA one of the rarest forms of 'lymphoma,' was described originally by Kundrat The literature on the subject is extraordinarily confusing On the one hand, the reader often has difficulty in being certain whether a given writer refers to true lymphosarcoma or some other variety of lymphoma, and on the other hand certain authors with easy disregard for exact nomenclature *and pathological entities include under the term lymphosarcoma many other quite* separate and distinct primary diseases of lymph nodes The situation is confused further by the fact that lymphosarcoma and lymphatic leukemia may coexist in a given patient, and that lymphatic leukemia may develop in a patient with lymphosarcoma whose blood previously had been entirely normal For these reasons only Kundrat's paper has been referred to, while there are many other articles of high merit in this field

Pathology

Lymphosarcoma is a highly malignant, invasive tumor composed of mature or immature lymphocytes We restrict the term lymphosarcoma to those cases which present a single invasive and destructive primary tumor While invasion of neighboring structures is common, metastases are rare, and widespread involvement of the lymphoid tissues is not found with the exception of those cases in which leukemia develops

Grossly the tumor varies somewhat in appearance In some instances, the lymph nodes can be recognized as such, although markedly enlarged in others their outlines cannot be distinguished The tumor then appears as a large, more or less homogeneous mass of tissue The color varies from white to pinkish to yellowish Areas of necrosis are not infrequent The consistence may be soft or fairly firm

Histologically, the tumor is composed of mature lymphocytes or of lymphoblasts *Mitoses usually are numerous Neither giant cells nor multinucleated cells* occur The structure of the involved lymph nodes is destroyed, and infiltration of the capsule is often present The reticulum is not increased but represents the normal reticulum of the lymph node The cells in true lymphosarcoma are uniformly round with rather scanty basophilic cytoplasm and a nucleus containing heavy masses of chromatin

Pathological Diagnosis

The greatest difficulty in differential diagnosis is found in distinguishing lymphosarcomas, especially the lymphoblastic type, from reticulum-cell sarcomas

In reticulum cell sarcoma, the cytoplasm is more abundant, irregular in shape, frequently amphophilic, or acidophilic, and occasionally shows evidence of amoeboid activity The nuclei of the reticulum cell sarcoma cells are several times larger than that of an adult lymphocyte irregular in shape, and their chromatin finely divided, unless the cells are extremely anaplastic While in many instances the diagnosis can be made from an eosin and methylene blue section, it should be emphasized that this is by no means always the case, and in the last analysis, the most important and reliable feature by which to make such differentiation is the distribution and amount of reticulum

In reticulum cell sarcoma, the reticulum is greatly increased, occurring as fine strands surrounding groups of cells and individual cells

In lymphosarcoma, on the other hand, the reticulum is scanty, representing the pre existing reticulum of the lymph node, as pointed out above

As has been said, lymphatic leukemia may develop in a case of lymphosarcoma This is a frequent event in childhood It is rare in adults

We should like to take occasion here to stress the fact that, in our opinion, the diagnosis of lymphosarcoma cannot be made on a section from a single, isolated, peripheral lymph node Histologically, the picture is identical with that seen in lymphocytoma with or without leukemia In order to arrive at a diagnosis, it is necessary to know the gross findings, as well as the histological appearance, of all the organs

In a series of 12 autopsies on cases of lymphosarcoma among 18 668 autopsies performed in the Boston City Hospital, the tumor was primary in the mediastinal nodes in 7 cases, in 2 cases, it was primary in the stomach, in 2 cases in the retroperitoneal nodes, and in 1 case in the cervical nodes In only 1 instance were there distant metastases, and these were to the kidneys from a tumor primary in the mediastinum However, involvement of the neighboring structures by extension and invasion by the primary tumor was common In the mediastinal group, the pleura, pericardium, and diaphragm were invaded frequently The

TABLE 1 *Lymphosarcoma Organs Involved Clinically (37 Adult Cases)*

	NO OF CASES
Lymph nodes	32
Tonsil	17
Mediastinum	15
Gastrointestinal tract	4
Bones	3
Lungs	2

tumors, usually massive in size also tended to cause compression of the great vessels The tumors primary in the stomach extended to the regional lymph nodes In the cases with retroperitoneal tumors the pancreas was invaded in both cases, the duodenum in 1, and the bone marrow in 1

Direct extension to neighboring organs is common, in the absence of leukemia metastases or widespread involvement is rare

It should be particularly noted that the bones and lungs are rarely involved and that, on the contrary, the tonsil is very often the site of the disease (Table 1) This is in sharp contrast to Hodgkin's granuloma

INCIDENCE

The age distribution of lymphosarcoma differs strikingly from other forms of malignant lymphoma It is commonest in early childhood and is again found in the later decades It is extremely rare between the ages of 20 and 40 (Table 2).

TABLE 2 *Lymphosarcoma Age Distribution (67 Cases)*

AGE	NO OF CASES
0– 9	28
10–19	12
20–29	0
30–39	1
40–49	4
50–59	8
60–69	9
70–79	5

The disease is definitely more common in males than in females, there being 41 males and 26 females in our entire series

SYMPTOMATOLOGY

The initial symptoms are rather strikingly different in the younger and the older patients In childhood petechiae or ecchymoses, pallor, and enlarged lymph nodes usually cervical were most often noted first and the initial complaints frequently were multiple

This initial symptomatology (Table 3) probably reflects the frequency with which leukemia is associated with lymphosarcoma in childhood

TABLE 3 *Lymphosarcoma Initial Symptoms during Childhood (30 Cases)*

	NO OF CASES
Petechiae or ecchymoses	22
Pallor	18
Enlarged lymph nodes	16
Splenomegaly or hepatomegaly	8
Skin nodules	6
Weakness anorexia etc	6

In adults the initial symptoms were more varied though far less liable to be multiple (Table 4) Abdominal pain loss of weight anorexia, epistaxis, vomiting and attacks of unconsciousness were seen occasionally The dyspnea may be extreme, and it should be noted particularly that persistent sore throat is a rather common symptom in elderly people

In children the course is rapid and the symptoms those of an acute form of leukemia plus those of an expansive tumor

TABLE 4 *Lymphosarcoma Initial Symptoms in Adult Life* (*37 Cases*)

	NO OF CASES
Mass in neck	9
Sore throat	5
Cough	4
Dysphagia	4
Dyspnea	3
Weakness	3
Abdominal pain	3
Loss of weight	2
Anorexia epistaxis vomiting unconsciousness	1 each

As the disease advances in adult life fatigue loss of weight cough sore throat dyspnea anorexia and abdominal pain become prominent It is noteworthy that in 13 of our 37 adult cases pleurisy with effusion developed and that in 8 of these the effusion was grossly bloody Bloody ascites developed in 4 of our cases Neither of these complications are common in other forms of malignant lymphoma Fever is not prominent as it is in Hodgkin's granuloma but a large variety of symptoms may develop among them exophthalmos enophthalmos edema epistaxis hematemesis melena hemoptysis and deafness Only 3 of our adult cases developed leukemia

Unless leukemia develops the peripheral blood picture shows nothing diagnostic or characteristic A moderate degree of anemia usually develops rarely it may be extreme Marked variation in the size and shape of the red cells is not unusual even though there is but slight anemia The percentage of polymorphonuclear leukocytes is usually elevated

ILLUSTRATIVE CASES

The following cases are illustrative of the course of the disease in adult life

A L (P 15171) A 17 year old boy was admitted to the hospital on 4 February 1939 Four months prior to entry he began to have a severe cough and increasing dyspnea On one or two occasions he spat up a small amount of blood The dyspnea increased steadily and the cough not infrequently was paroxysmal

Upon entry he was extremely orthopneic and cyanotic By x ray there was marked widening of the mediastinum and paracentesis showed a massive bloody effusion in the right chest This was aspirated cautiously and over a period of several days a total of 2 700 cc was removed There were a number of rather firm small nodes in each side of the neck and in each axilla There was marked congestion and slight edema of the face and neck Both the red blood and white blood cell pictures were essentially normal Biopsy on 9 February showed lymphocytoma

He was given 800 r of high voltage x ray to the mediastinum and 400 r to each side of the neck The response was dramatic and he was discharged a month after admission The mediastinal mass as well as the effusion had practically disappeared and the patient felt well

A month later however in April 1939 he was readmitted for extreme weakness and dyspnea The mediastinal nodes once more were markedly enlarged

Further x ray therapy produced no apparent benefit

In June 1939, four months after entry, the patient's white blood cell count suddenly rose to 51,000, and coincidentally the percentage of lymphocytes rose to 79 He had numerous nose bleeds The white cell blood count increased to 104 000 The red blood cell count fell to 1,700,000, and the patient died 29 June 1939, eight months after the first symptoms properly attributable to his disease

T L (H 30–385) A 75 year old man was admitted to the hospital on 26 March 1930 Six months previously he noticed a 'growth on his right tonsil' The mass gradually increased in size, and two weeks before entry it became definitely painful There were no other physical findings worthy of note Biopsy on 3 March showed lymphocytoma

He was given 1,200 r of x ray to the right side of the neck, and thereafter the lymph nodes disappeared, and the tonsillar mass diminished greatly in size

therapy, but six months later, all reappeared

In spite of repeated doses of high voltage x ray, the nodes continued to increase in size, and the patient became rapidly weaker

He died suddenly on 16 May 1931, one year and nine months after his first symptom

Course and Treatment

The course of the disease is almost always progressive to death Great alleviation of symptoms, and marked improvement in health may follow x ray therapy The results, however, are but transitory, and it often seems that the more favorable the initial treatment, the sooner the disease will return

Aside from appropriate high voltage x ray, 400 to 1,600 r at proper intervals, there is little to be offered other than symptomatic relief Transfusions are, of course, indicated, if the red blood-cell count falls, or if a bleeding tendency develops, as it so frequently does in children

The question of radical surgery is a moot one We have never seen a case suitable for such therapy There are a number of reports of successful excision of a localized lymphosarcoma and radical surgery might well be indicated in certain cases, though a careful scrutiny of the case reports in the literature leaves some doubt about whether these patients had lymphosarcoma or reticulum-cell sarcoma the latter a condition in which we do believe that radical surgery may rarely result in a cure

Prognosis

Lymphosarcoma kills rapidly, especially in childhood No case under 12 years of age lived more than eight months, most were dead in four months In the older age groups, an occasional case will live three or even four years from onset (Table 5)

TABLE 5 *Lymphosarcoma Duration from Onset to Death (67 Cases)*

AGE	DURATION (MONTHS)	AVERAGE DURATION (MONTHS)
0–15	1–8	5
16–40	2–30	5
41–75	1–50	17

It is well to remember that as in other forms of malignant lymphoma sudden death may ensue, even though the patient appears to be in comparatively good health

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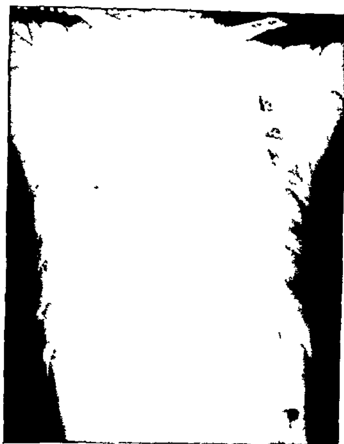
Kundrat H Ueber Lymphosarkomatosis *Wien klin Wochnschr*, 1893 6 211

PLATE XII

LYMPHOSARCOMA INVASION OF MYOCARDIUM

LYMPHOSARCOMA RETICULUM STAIN

PLATE XIII



Lymphosarcoma before treatment



The same case after treatment

V

Giant Follicle Lymphoma

GIANT FOLLICLE lymphoma or follicular lymphoblastoma was described first by Brill Baehr and Rosenthal in 1925 under the noncommittal term giant lymph follicle hyperplasia

In 1932 Baehr reported 19 cases and discussed in some detail the clinical findings and the histological picture At that time he wrote Follow up observations of 19 cases indicate that the condition is a distinctive form of lympho sarcoma which may manifest more malignant and invasive characteristics later in the disease Thus for the first time there arose the suspicion that giant follicle lymphoma might be the prelude to a more serious condition A similar point of view has been expressed by Sugarbaker and Craver and has been reiterated by Baehr and Klemperer We agree that the condition is potentially malignant in the sense that it frequently develops into some other and fatal form of malignant lymphoma Extremely rarely it may be fatal even though the histological picture has not changed in type It can never be safely regarded as benign

PATHOLOGY

The characteristic histological feature of the classic type of giant follicle lymphoma is the large number of huge lymphoid follicles often visible with a hand lens in a fresh specimen or in a stained section The greatly enlarged follicles virtually fill the entire lymph node compress the surrounding pulp and often break through the capsule into the surrounding tissue The center of these follicles is filled with actively proliferating cells either lymphocytes and their predecessors or more rarely, reticulum cells Although occasional polymorpho nuclears and monocytes are present also the uniformity of the predominant cells within the enlarged follicle is notable and important Sometimes though not invariably the enlarged follicles are surrounded by a narrow zone of closely *packed mature lymphocytes Phagocytosis by the reticulum cells very rarely* occurs a point of considerable importance in differentiating this disease from simple inflammatory conditions in which phagocytosis of nuclear debris and cellular pleomorphism are common Silver stains show strands of reticulum surrounding and outlining the enlarged follicles and demonstrate clearly the compression of the pulp The usual amount of reticulum is seen within the follicles The involved lymph nodes usually are discrete

The disease must be differentiated from chronic non specific inflammatory conditions of the lymph nodes Uniformity of the cells within the follicles lack of phagocytosis and invasion of the capsule all favor the diagnosis of giant

follicle lymphoma It is well to remember also that chronic enlargement of lymph nodes in an adult only rarely is due to inflammation alone, unless the causative infection is obvious

The lymphadenopathy may be generalized but more commonly appears to be confined especially in the early stages of the disease to a comparatively small region Internal organs such as the spleen and more rarely the liver, bone marrow, breast, and other structures, are involved occasionally even in the uncomplicated disease

It has been said already that the predominant cell in the enlarged follicles may be the lymphocyte or the reticulum cell Baehr believes that the condition is a form of lymphosarcoma and further states that in the terminal stage of the disease they have twice observed a marked increase in leukocytes and the appearance of lymphoblasts in the blood stream It is our experience, too, that in certain cases the condition develops into lymphosarcoma, the type cell then being the lymphocyte or lymphoblast.

Similarly, though less often, there may arise subsequently from the predominant reticulum cells a reticulum-cell sarcoma or, presumably from the same cell Hodgkin's disease of one or the other type This metamorphosis into a more malignant disease may be seen occasionally in some small portion of an excised lymph node when the patient is first seen or it may occur months or years later, when all histological evidence of the original giant follicle lymphoma has disappeared. It is obvious that two or more biopsies or a biopsy and subsequent autopsy are necessary to combat the claims made by some that such changes are fortuitous

In our own series of 39 cases, there were 25 that, at the time of biopsy, showed the characteristic picture of giant follicle lymphoma as originally described by Baehr Ten remained giant follicle lymphoma as far as could be told The remaining 15 cases of this group of 25 did not fare so well, for later biopsy or autopsy showed that 7 had developed Hodgkin's granuloma, 4 had changed into lymphosarcoma 2 into reticulum cell sarcoma and 2 into Hodgkin's sarcoma

Fourteen cases showed at the time of first biopsy, evidences of transformation into some other type, that is within the node showing the characteristic picture of giant follicle lymphoma, there were small areas having the histological features characteristic of some other form of malignant lymphoma In 10 the picture was that of a lymphosarcoma In 2, there was unmistakable evidence of Hodgkin's granuloma and in 1 each were seen the features of reticulum cell sarcoma and Hodgkin's sarcoma In every instance the subsequent course of the disease was that of the particular form of lymphoma evidenced by the first biopsy

Baggenstoss and Heck report 2 cases in which subsequent biopsies revealed the histological picture of lymphosarcoma, though traces of the follicular structure could still be found'

It is evident therefore that while giant follicle lymphoma is a comparatively benign condition there is a strong tendency for the condition to become malignant, for 36 per cent of our patients eventually developed 'lymphosarcoma,' confirming Baehr's contention that giant follicle lymphoma is a specialized form

of that disease, and in 29 per cent more, one or another form of lymphoma developed.

Incidence

Giant follicle lymphoma is most common in middle-aged and elderly people, though it may be seen at any age (Table 1) All of our patients were over 20 years as were Baehr's, Baehr reported cases from the age of 20 to 68 with an average age of 42 years Baggenstoss and Heck cite a case of a 2 year-old child The rarity in the first decade of life of giant follicle lymphoma in comparison to the occurrence of simple inflammatory conditions of the lymph nodes on the one hand and the occurrence of lymphosarcoma, lymphatic leukemia, and Hodgkin's granuloma on the other is worth more than passing notice from the diagnostic point of view

Table 1 *Giant Follicle Lymphoma Age Distribution* (*39 Cases*)

AGE	NO OF CASES
0–9	0
10–19	0
20–29	4
30–39	3
40–49	6
50–59	17
60–69	6
70–79	3

The condition is slightly more common in men than in women

Symptomatology

The onset is insidious the initial symptom being most commonly painless enlargement of the superficial lymph nodes which are discrete, soft or rubbery, and nonadherent It is worth noting that inguinal lymphadenopathy is far more common early in the disease than in other forms of lymphoma Systemic symptoms such as fever and loss of weight are rare (Table 2), though 4 of Baggenstoss and Heck's patients had an initial complaint of weakness

Anemia does not develop, unless complications occur to cause anemia, and the white blood cell count and the differential cell count are normal, unless lymphatic leukemia develops a complication which has been reported, although we personally, have not seen it

Table 2 *Giant Follicle Lymphoma Initial Symptoms* (*39 Cases*)

	NO OF CASES
Inguinal lymphadenopathy	17
Cervical lymphadenopathy	14
Axillary lymphadenopathy	2
Pain in abdomen	2
Edema of legs	2
Loss of weight	2
Multiple symptoms	1

Diagnosis

The disease in its simple and uncomplicated form may be confused with acute and chronic inflammatory lymphadenitis, Hodgkin's disease tuberculosis, lymphatic leukemia, and indeed with any condition causing painless enlargement of superficial lymph nodes without other symptoms of note It is obvious, therefore that the diagnosis can be made only by careful histological examination of an excised lymph node In some cases, the differential diagnosis between the disease and a simple inflammatory condition may be impossible Under these circumstances, the patient must be watched carefully over a period of time and subsequent biopsies taken if it seems wise From a clinical point of view, the larger the nodes, and the more generalized the lymphadenopathy, the more liable the diagnosis of giant follicle lymphoma is to be correct

Course of Disease

The course of the disease naturally is variable and depends to a large extent upon whether or not the initial, simple giant follicle lymphoma is replaced subsequently by some other form of lymphoma

In those cases showing only uncomplicated giant follicle lymphoma, there is usually painless lymphadenopathy, most frequently in the inguinal or cervical regions The lymph nodes are soft or rubbery, discrete, and unattached to the surrounding tissues Occasionally they are tender In 12 of Baehr's 19 cases, the spleen was enlarged Baggenstoss and Heck state that 'the spleen is usually greatly enlarged' Splenomegaly in our own experience has been less frequent Four of 10 cases, which apparently remained simple and uncomplicated, had clinical evidence during life of enlargement of this organ Hepatomegaly is still more unusual In a few cases, there is loss of weight, anorexia, or abdominal distress, the latter symptom presumably being due to enlargement of retroperitoneal nodes Baehr noted that compression symptoms might occur and further found unilateral exophthalmos in 4 of his 19 cases Baggenstoss and Heck stress the frequency of serous effusions in pleural and peritoneal cavities This complication was found in 6 of our 39 cases So far as our own experience goes, in the pure form of giant follicle lymphoma, the blood picture remains essentially normal

In short, we believe that in patients suffering from the uncomplicated condition, such symptoms as they have are due to the presence of painless, though often generalized, lymphadenopathy It should be emphasized that often the lymph nodes regress spontaneously for a time and thus lull both the patient and the physician into a false sense of security Such temporary regression even though of comparatively long duration, is not uncommon Should some other form of lymphoma develop, signs and symptoms of that disease are not slow in appearing, and the occurrence of such symptoms and signs, such as marked loss of weight, hematemesis, fever, bloody pleurisy with effusion and the like, call for a careful re evaluation of the patient's prognosis and treatment

Illustr[illegible] ases

The course of the simple disease is [illegible] by the following cases

W G (P 13394) This 65 year-old man noticed early in 1932 painless swellings in the right side of the neck and right groin These continued with minor exacerbations and remissions until 1934 In December of that year he was admitted to the hospital Physical examination at that time revealed a few olive sized lymph nodes of firm consistence in both sides of the neck and both axillae In either groin were walnut sized discrete non tender rubbery lymph nodes The spleen was readily felt 2 cm below the costal margin Otherwise the physical examination was essentially normal The blood picture was not unusual Biopsy (P S 37–1336) showed typical giant follicle lymphoma The patient was given 400 r of x ray to each of the involved areas with complete disappearance of all lymphadenopathy He was alive and well when last seen in October 1942 ten years from the onset of his disease

R Z (Pv 33) This 21 year-old single man noted in November 1933 enlarged painless though rather massive lymph nodes in the right groin There were no other symptoms The nodes were discrete and rubbery The remainder of the physical examination revealed no abnormalities One of the nodes was excised and showed the microscopical picture typical of giant follicle lymphoma He was given approximately 400 r of x ray to the involved area and has remained symptom free to October 1946

It is evident from what has been said already that giant follicle lymphoma frequently is but a prelude to adventure and that the pathological process frequently becomes altered with the passage of time Under these circumstances it is obvious that there will develop the symptoms and signs of that form of lymphoma into which the disease is progressing Such a train of events is illustrated by the following cases

I P (H 36–1292) This 54 year-old woman was admitted to the hospital in December 1936 The preceding June she had noticed a painless lump in the right axilla Six months later the mass rapidly increased in size and became very tender Under rest and local applications of heat the mass decreased in size and the pain disappeared A biopsy at this time revealed the presence of a typical giant follicle lymphoma (T S 37–651) Apparently all the involved lymph nodes were removed The physical examination revealed nothing other than hypertensive heart disease The patient was given 400 r of x ray to the right axilla *Except for minor symptoms unrelated to her fundamental disease* the patient remained well until March 1939 when on routine physical examination there was found a mass of nodes deep in the right pelvis and in the right groin The patient was given 1 000 r of x ray to the involved areas and remained well

clinic and was obviously very much worse There were enlarged rather soft non tender lymph nodes in either side of the neck The mass to the right of the umbilicus had increased considerably in size A gastrointestinal series of x rays showed an extensive mass pressing upon the hepatic flexure of the colon The patient complained of anorexia dysphagia and fleeting pains deep in the ab-

domen She had lost 30 pounds in weight The peripheral blood which heretofore had been essentially normal now showed a moderate degree of hypochromic anemia the red blood cell count being 4 000 000 and the hemoglobin 63 per cent The white blood cell picture still remained normal She was given 700 r of x ray to the abdomen and 450 r to the neck There was however no relief from symptoms The abdominal distress continued the dysphagia increased and there developed marked dyspnea with inspiratory stridor This latter symptom increased rapidly and the patient died of asphyxia in October 1939 two and a half years after the discovery of the giant follicle lymphoma and four months after the rather sudden development of symptoms which proved refractory to x ray therapy

Autopsy showed Hodgkin's sarcoma involving the cervical mesenteric and peripancreatic lymph nodes with metastatic lesions in the thyroid and kidney and direct extension from the mesenteric nodes to the hepatic flexure of the colon

Another case C H (S D 386) had in 1931 painless enlarged cervical lymph nodes which proved on biopsy to be giant follicle lymphoma (S 31–2457) They were treated with moderate doses of x ray and the patient remained well until 1936 when she re entered the hospital with symptoms consistent with carcinoma of the stomach She died shortly thereafter and the autopsy (A 36–449) showed a Hodgkin's granuloma involving the mesenteric lymph nodes and secondarily the duodenum

We have had but one case in which the disease remained pure giant follicle lymphoma from onset to death

J B (B C H 1106907) This 33 year old married man first entered the hospital on 19 November 1942 with generalized enlargement of the lymph nodes which were rubbery in consistence freely movable and non tender The largest node measuring 9 x 4 cm was in the right inguinal region There were other nodes about 4 cm in each axilla and in the right supra and infra clavicular regions The liver was 7 cm below the costal margin in the right mid-clavicular line extending across the midline and non tender The spleen was 14 cm below the costal margin in the left mid clavicular line Its border was rounded The abdomen was markedly distended and tense Appropriate amounts of high voltage x ray were given to the involved areas and the patient improved greatly

The patient gave a history of symptoms consistent with gastric ulcer In 1941 he noted painless nodes in the right inguinal region Three months before entry there was progressive enlargement of the abdomen and marked discomfort after eating For two or three months he had had marked increase in sweating increasing weakness and fatigability and increasing dyspnea on exertion

A total of 1 000 r of x ray was given to the spleen and 900 r to each groin between 24 November 1942 and 2 January 1943 On 31 December 1942 a lymph node removed from the left supraclavicular region was reported as showing giant follicle lymphoma About two weeks after irradiation was completed the patient began to improve and was able to be up and about He was discharged after thirteen weeks in the hospital

He felt very well for a few weeks and then began having sharp pain in the posterior chest and steady severe pain in the right upper quadrant of the abdomen There was also progressive enlargement of the abdomen dyspnea weakness and sweats He noted no enlargement of the lymph nodes After three

months at home he was referred back to the hospital because of his poor condition

On this admission examination was essentially the same as before except that the liver was 10 cm below the ribs and its contour appeared to be somewhat irregular The spleen was 5 cm below the umbilicus No particular change was noted in the lymph nodes

The patient had little appetite he continued to be uncomfortable from abdominal swelling and sweated a great deal On the eighth hospital day he developed pneumonia and died on the thirteenth hospital day six months after his first hospital admission and approximately two years after the onset of giant follicle lymphoma the only pathological condition other than the pneumonia found at autopsy (A-43-356)

Treatment

The treatment of giant follicle lymphoma is prompt irradiation to such therapy the condition responds favorably as Baehr has pointed out

Lymph nodes involved by pure giant follicle lymphoma are commonly very sensitive to x ray and 200 to 400 r to each portal is often sufficient to bring about their complete disappearance Further radiation should be withheld until additional signs and symptoms appear at which time a second biopsy should be done if a superficial lymph node is accessible in order to rule in or out the development of some other form of malignant lymphoma If the disease remains uncomplicated subsequent x ray treatments may be moderate If however by biopsy or *clinical evidence it appears that some other type of lymphoma has appeared* correspondingly heavier doses should be used It is possible that radical surgical intervention might bring about better results provided the disease process is sharply limited to one readily accessible area though we have no very good evidence that such is the case All foci of infection should be removed if possible

Prognosis

The prognosis of giant follicle lymphoma is varied and depends in large measure on whether the type changes or not So long as the disease remains simple and uncomplicated the outlook is fairly good the average duration being in the neighborhood of six years and a small number of cases are alive and free from symptoms as long as ten years after their initial symptom If however the type changes the prognosis becomes that of the newly developed condition In all cases the prognosis must be guarded Sudden death may occur though it is very rare

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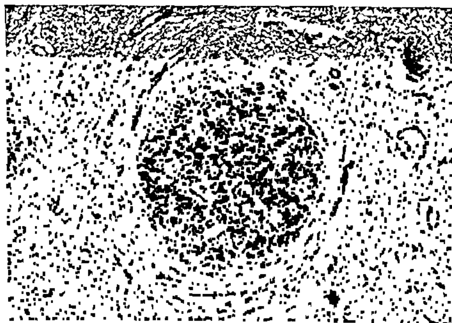
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PLATE XIV

Giant follicle lymphoma of lymph node.



Giant follicle lymphoma Reticulum stain

VI

Plasmocytoma

TUMORS COMPOSED of plasma cells are relatively uncommon They are most frequently primary in the bone marrow and, as such, constitute the majority of multiple myelomas These are classed by many authors among the bone tumors (Aschoff, Borrmann, Ewing) Others are inclined to regard plasmocytomas as more closely allied to the leukemias and thus to diseases of the blood forming organs in general (Lubarsch, Pappenheim, von Witzleben)

Various considerations support the view that multiple myeloma is a systemic disease not necessarily confined to the bone marrow Generalized diffuse myelomas have been described by Berblinger, Enneking, Helly and Schmidtmann, and it is common experience that the tumors may be multiple and discrete or diffuse to a greater or lesser extent Extraosseous metastases have been described by several authors (Battaglia, lit, Bertrand, Soupault and Gutmann, Geschickter and Copeland, lit Hoffmann Maresch)

Extraosseous plasmocytomas have been frequently described, but, as Ewing pointed out, these tumors in general have received inadequate attention and are commonly — though erroneously — classified as lymphosarcomas In a recent review of the literature, Hellwig was able to collect 127 extramedullary plasmocytomas and added one case of his own Of these tumors, 64 originated in the air passages 47 in the conjunctivae, 4 in lymph nodes, and 13 in other organs Hellwig like Ewing, felt that these tumors have received inadequate attention and he believed that this was due in great part to the fact that most reports have been descriptions of single cases and have appeared in journals devoted to the surgical specialties Only brief mention is made of these extramedullary tumors in the general textbooks of pathology

Plasma cells in the blood have been described from cases of apparently typical multiple myeloma (Beck and McCleary, Ghon and Roman) In a recent report, Meyer, Halperin, and Ogden cite 25 cases of plasma cell leukemia from the literature and add one of their own These authors believe that all the reported cases of plasma-cell leukemia represent cases of multiple myeloma with an associated leukemia

It would seem then that, as various writers have pointed out there are gradations in plasma-cell tumors similar to those of the other so-called lymphomas They may be single or multiple, relatively benign or highly malignant, and further may be associated with a leukemic blood picture

In our series of 67 cases, 5 were extraosseous and 62 intraosseous

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Intraosseous plasmocytomas have been repeatedly and fully described both in

general reviews and in textbooks Therefore we plan to concern ourselves only *with the extraosseous* plasmocytomas

Pathology

Plasmocytomas are soft to moderately firm in consistence Their color varies from grayish white to grayish red The type cell is the plasma cell. Plasma cells are thought by many workers to be derived from lymphocytes and in that we concur The typical plasma cell is round to oval to polyhedral in shape measuring 9 to 11 μ in its greatest diameter The cytoplasm is homogeneous and is basophilic There is usually a perinuclear clear zone in which the centrioles may frequently be distinguished The nucleus is eccentric and contains chromatin arranged in clumps at its periphery which has led to the descriptive term of cartwheel nucleus The number of nuclei in a cell varies from one up to three or four

As a rule mitotic figures are not numerous In the more rapidly growing and anaplastic tumors the cells are larger and multinucleated giant forms are not uncommon These giant cells bear a superficial resemblance to megakaryocytes and to Reed–Sternberg cells

Stained supravitally with neutral red and janus green the cytoplasm of the plasma cell has a slightly brownish tint and contains many rod shaped mitochondria especially in the neighborhood of the nucleus Granules staining with neutral red are few in number or entirely absent The plasma cell gives a negative peroxidase reaction

There is no increase in reticulum

Illustrative Cases

Case 1 E K (H H–21–1118) a married Norwegian painter aged forty six years entered the Collis P Huntington Memorial Hospital on 21 September 1921 complaining of a recurrent growth in his throat

During the early years of his life he had been in general very healthy and he remembered no childhood diseases

In 1918 three years before entry to the Huntington Hospital he had a painless tumor removed from the left tonsillar region at the Massachusetts Charitable Eye and Ear Infirmary

First Biopsy The pathologic report on this specimen (M G H 6 February 1919) was A tumor about 2 inches in its greatest diameter partly invested with mucosa and with some muscle tissue adherent On section it is composed of soft grayish tissue Microscopic examination shows the tumor to consist of closely packed cells and very little stroma The cells are generally small and have indistinct scanty protoplasm They seem to belong to the lymphocyte series and are atypical Only one mitotic figure found There is some infiltration of the muscle by tumor cells

Diagnosis Lymphoma probably of low grade malignancy"

Second Biopsy A year later a similar mass was removed from the right side of his throat (Brooks Hospital 27 January 1920) The pathologic report follows This is a small definitely circumscribed mass made up chiefly of small round or slightly elongated cells probably of the lymphocyte series *It is evi*dently of very slow growth as no mitotic figures could be found There is evi

dence of inflammatory reaction about the periphery It may be a slowly growing lymphoblastoma There is also a possibility, though this seems remote, of myeloma An examination of the urine for albumose might help in diagnosis'

We have been able to examine the microscopic sections from this biopsy specimen and the histologic picture is identical with that of his third biopsy specimen described below

After these operations he remained symptomless until eight months before

obstruction to swallowing There were, however, no general symptoms and his general physical condition was excellent

On entry the right tonsillar region was found to be occupied by a smooth, firm spherical tumor measuring 3 5 cm in diameter The remainder of the physical examination was normal He weighed 175 pounds The white blood cell count was at the time of admission 8200 per c mm and the differential showed 65 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 28 per cent lymphocytes and 5 per cent monocytes No abnormal or young cells were seen The red blood cell count was normal but the red blood cells were slightly achromic The urine was negative

A clinical diagnosis of lymphosarcoma was made and three radium seeds, of 2 m c each were inserted deep into the tonsillar mass Under this treatment the tumor receded markedly in size There were no signs or symptoms pointing to generalized involvement

The patient remained symptomless and apparently healthy for the next five years

the past few weeks he had also had a dull, continuous headache in the frontal region

Physical examination at this time showed him to be well developed and nourished There was a small ulcer just above the epiglottis, presumably an aftermath of the former radium treatment The original tonsillar tumor had not returned There were no palpable lymph nodes in any region No abnormalities were found elsewhere The blood at this time showed a red-cell count of 3 950 - 000 per c mm with a hemoglobin of 95 per cent There were 11 800 white blood cells per c mm with 75 per cent polymorphonuclears, 14 per cent lymphocytes, and 11 per cent monocytes The urine was entirely normal A Roentgen ray film of the lumbar vertebrae and the sacroiliac regions showed no abnormalities other than slight hypertrophic changes such as might be seen in any man of his age Acting on the belief that the pain was due to enlarged metastatic retroperitoneal lymph nodes, a full 'suberythema' dose of Roentgen ray was given over the sacroiliac region and another a month later Following this second treatment there was marked relief from the pain The patient remained symptomless until March 1926 At this time examination of the throat showed once more a bulging of the left tonsillar fossa and bean sized lymph nodes, soft discrete, and freely movable in the right posterior cervical chain There were, however, no symptoms of importance

In May 1926, he returned to the clinic complaining for the first time of sharp pain in the left chest There was some tenderness in the seventh interspace in the anterior axillary line Nothing abnormal, however, was found by the Roentgen ray, though a few crackling râles were heard on inspiration at the bases of both lungs There was no friction rub Two days later, he fell from a step ladder, striking his left chest There was tenderness over the tenth rib near the spine and Roentgen rays showed a fracture of this rib but no other ab normalities This fracture healed, the pain in the chest disappeared completely, and it was not until October 1926, that he returned to the clinic. The pain in the chest had returned and there was a loose troublesome cough Bence Jones protein was for the first time, noted in the urine The blood picture remained essentially normal except for a slight secondary anemia Roentgen ray examination of the chest showed for the first time eight and a half years after the initial throat tumor circular areas of diminished density throughout the ribs and pelvis, suggestive but not entirely characteristic, of multiple myeloma He received one half a 'suberythema' dose over the anterior chest and the pain entirely subsided There followed an eight month interval during which he remained free from symptoms except for an occasional cough

In June 1927, the cough became more severe, and there was a constant aggravating pain in the right posterior chest A moderate amount of dyspnea was also complained of for the first time The lungs showed on examination slight dullness at both bases with fine crackling râles The urine contained much al bumin and a few granular casts The Roentgen ray films, taken at this time, showed numerous, small, rounded areas of diminished density in the ribs, skull, ilium and right and left femurs The white blood cells remained essentially normal, but the red blood cell count had fallen to 2 640 000 per c mm and the hemoglobin to 66 per cent A full 'suberythema' dose of Roentgen ray was given over the chest both front and back, and in a week the pain in the chest had dis appeared, though the cough and dyspnea to a large extent remained The patient remained essentially symptomless except for an occasional cough and some troublesome but not severe, pains in the lower back and chest, which persisted un til his death

In January 1928 he again received a full 'suberythema' dose of Roentgen ray over the chest as the pain and cough had increased This treatment to a certain extent relieved his symptoms but the râles and dullness persisted at both bases

Third Biopsy In May 1928, a lymph node was removed from the left side of the neck (S–28–1256) The pathologic report follows 'The specimen consists of several fragments of reddish brown tissue, irregular in shape The largest measures 1 cm by 0 5 cm by 0 5 cm, and the smallest 0 5 cm by 0 5 cm by 0 3 cm On section the tissue cuts with difficulty Microscopic examination shows the normal structure of the lymph node is completely lost due to a diffuse infiltration with tumor cells Only in a few areas can small focal collections of lymphocytes be distinguished At several points at the periphery the tumor cells have invaded the capsule and are growing in the surrounding fat and connective tissue The tumor cells are polygonal or stellate in shape and are somewhat larger than small lymphocytes Their cytoplasm is basophilic and contains, near the nucleus, a small clear area in which can be seen the centrioles Their nuclei which are eccentrically placed are round with a thick nuclear membrane and heavy masses of chromatin often arranged at the periphery A considerable number of the cells are binucleate and some contain three and four nuclei In general, the cells

do not vary much in size but an occasional large cell with a correspondingly large nucleus can be found Mitotic figures are present but are extremely rare Scattered among the tumor cells are a few macrophages, containing blood pigment

Diagnosis A slowly growing plasmocytoma'

Supravital studies employing as stains neutral red and janus green were also made on this specimen The tumor cells appeared as medium sized polygonal cells with eccentrically placed nuclei The nuclei contained large masses of chromatin The cytoplasm of the cells had a slightly brownish tinge and showed many rod shaped mitochondria especially in the neighborhood of the nucleus The cells contained few or no neutral red granules These cells were identical with those of a myeloma of the humerus studied in the same manner

Smears of the lymph node were also made and stained with Wright s stain and with Sato and Sekiya s peroxidase stain In the preparations stained with the former the tumor cells looked like typical plasma cells They gave a negative peroxidase reaction

At this time his red blood cell count was 2 380 000 per c mm hemoglobin 60 per cent The white blood-cell count was 9150 per c mm with 82 per cent polymorphonuclears 2 5 per cent eosinophils 2 5 per cent basophils 5 per cent lymphocytes and 9 per cent monocytes There was apparent some loss of weight For the first time he seemed to be definitely losing ground He had become quite weak the cough was aggravating and came in paroxysms which were most painful and which could be controlled only by codein Dyspnea was constant though not marked There was slight pitting edema of the ankles Bean sized lymph nodes were found in the left and right posterior cervical chains and in the right axilla They were soft discrete freely movable, and non tender No tumor was apparent in the throat The lungs showed dullness and râles at both bases The liver was just palpable on gentle inspiration The spleen could not be felt

By August 1928 the anemia had become more severe The red blood cell count was 2 190 000 per c.mm , the hemoglobin 43 per cent. A diffuse brownish pigmentation had appeared all over the body especially on the face and neck There was extreme pain in the left posterior axillary line at the eleventh rib with tenderness over the same area The pain in the left hip and leg had returned in aggravated form Walking was impossible without a cane There was marked [illegible] gion [illegible] the [illegible] con trolled by codein only

In October 1928 he had a severe nosebleed from the right nostril for which no further cause could be found than a small ulceration on the septum This bleeding continued intermittently until his death though it was never severe enough to aggravate his already existing anemia

In January 1929 he had become much weaker Pallor was striking and cachexia marked The brownish pigmentation of the skin appeared more noticeable perhaps because of the increasing pallor The superficial lymph nodes in the axillae and neck did not increase in size A few râles and some dullness were still present in both bases of the lungs The liver reached 8 cm below the costal margin but the spleen could not be felt There was well marked pitting edema of the ankles The urine continued to show albumin in large amounts Bence Jones

protein and many finely granular casts An occasional red cell was seen The temperature was normal The white cells numbered 5620 per c mm with 67 per cent polymorphonuclears 3 5 per cent eosinophils, 1 5 per cent basophils 10 5 per cent lymphocytes and 17 5 per cent monocytes The red blood cells were 2 000 000 per c mm with a hemoglobin of 43 per cent A two hour renal function test showed fixation of specific gravity at 1 010 with a day excretion of 1200 cc and a night urine of 1100 cc The blood nonprotein nitrogen was 36 8 mg per 100 cc He was so weak that he was admitted to the hospital On entrance breathing was slow and stertorous He was drowsy most of the time but no ab normal neurologic signs were elicited The sclerae were icteroid The heart was normal The blood pressure was 142/60 The lungs showed dullness at both bases with many fine crackling râles The liver was palpable 4 cm below the ribs He gradually became more drowsy and could be roused with difficulty The blood nonprotein nitrogen rose to 130 mg per 100 cc He gradually became worse and died on 2 February 1929 eleven years after the removal of the first tumor

Autopsy (H H 29–338) showed multiple myeloma involving the ribs right radius and lumbar vertebrae hypertrophy and dilatation of the heart and gen eralized arteriosclerosis All the ribs showed fusiform enlargement at one or more places On section these enlarged portions were found to consist of a thin bony shell enclosing a cavity filled with soft fleshy red tissue

Microscopic examination of a section of a rib showed the marrow cavity filled with tumor cells of the same type as described in the preceding lymph node biopsy (S–28–1256) No normal marrow cells were made out The cortex of the bone showed marked thinning and at one place the tumor had broken through and was invading the adjacent striated muscle

CASE 2 M R a married man aged 53 years entered the Boston City Hos pital in April 1929 complaining of a lump in his neck In addition for some time he had had pain in his left hip The past history was entirely negative Roentgen rays of the bones showed only hypertrophic changes in the left hip joint There was a moderately hard freely movable mass low and anteriorly in the right side of the neck This was removed and proved to be a plasmocytoma (S 29–1186) of the thyroid Two months later the pain in the leg was much more severe and Roentgen rays then showed a few small circular areas of destruction in the left iliac crest and left femur There was no anemia no ab normalties in the white cells and the urine showed a small trace of albumin but no Bence Jones protein The blood pressure was normal A month later the bone lesions demonstrable by Roentgen ray had spread to the ninth dorsal spine and bean sized lymph nodes soft and freely movable had appeared on both sides of the neck both anterior and posterior to the sternomastoid muscle The pain in the leg became more severe

In August the pain in the right hip and leg was more severe and he was un able to walk There was exquisite tenderness over the right sacroiliac joint At this time Roentgen ray showed several small sharply defined areas of destruc tion in the skull ninth dorsal and third lumbar vertebrae and in the ninth and tenth ribs There were irregular areas of destruction in both iliac crests and the left ischium The findings were considered by the roentgenologist more charac teristic of metastatic malignancy than of myeloma Bence Jones protein was found for the first time in the urine High voltage Roentgen ray treatments were

given with but slight improvement The patient continued to have considerable pain, and subsequent Roentgen rays showed a spread of the lesions In October 1929 the patient was considerably worse There was marked loss of weight and a definite secondary anemia The red blood cells were 3 000 000 per c mm, the hemoglobin 65 per cent The white blood cells were 5200 per c mm The differential count showed 68 per cent adult polymorphonuclears 7 per cent young polymorphonuclear neutrophils 1 per cent eosinophils 10 per cent lymphocytes and 13 per cent monocytes Roentgen rays demonstrated a marked spread of the bone lesions The pain in the hip and leg became progressively worse The lymph nodes in the neck enlarged considerably and there appeared in the right midabdomen a progressively enlarging firm mass reaching the size of a grapefruit It appeared to be retroperitoneal but was not fixed Enlarged lymph nodes appeared in both groins The patient became increasingly weaker and died in November 1929 Unfortunately no autopsy could be obtained

Case 3 * A O a married woman aged 67 years entered the Carney Hospital on 17 July 1927 complaining of a mass in the neck

The past history was essentially negative

Six months before entry the patient noticed a small painless mass beneath the left ear This increased in size and was accompanied by sharp pains radiating down the side of the neck and to the left occipital region On entrance there was found in the left side of the neck, posterior to the sternomastoid muscle a freely movable firm walnut-sized tumor No other masses were noted There was a marked secondary anemia with a red-cell count of 2,560 000 per c mm and 30 per cent hemoglobin The white-cell count was 5000 per c mm and the differential count was normal The mass in the neck was excised (S-28-1706) and proved to be a plasmocytoma identical histologically in all respects with the tumors removed from the other 2 patients The urine showed a trace of albumin Roentgen rays of the bones however showed no involvement and there were no symptoms suggesting classical multiple myeloma There was an uneventful recovery from the operation, and the patient was known to be well and symptomless nearly three years later No local recurrence had been noted.

Case 4 C F a male aged 64 years entered the Pondville Hospital on 28 February 1929 (No 1183) The past history was negative One sister had died of cancer

Two years before entry a small soft lump appeared on the anterior surface of the upper gum The mass was treated with radium and temporarily disappeared but a few months later he noticed that his upper lip and right side of his nose were being pushed out Since that time the tumor gradually grew and at the time of entrance to the hospital was of sufficient size to cause some obstruction to breathing

Complete physical examination on entrance was negative except for a blood pressure of 220 120 and a moderately enlarged heart There was a soft tumor partially replacing the upper alveolus extending forward onto the upper lip and backward one third the distance of the hard palate The nasal septum was pushed to one side and the tumor mass nearly completely blocked the posterior nasal opening There were no enlarged lymph nodes nor any abdominal

* We are indebted to Dr Francis Nash for his kind permission to publish the report of this case

masses Under colonic ether, the mass was removed almost in its entirety It proved to be a plasmocytoma (H S 29-1503)

The urine was negative There was no anemia and the white blood count was normal Roentgen rays of the skull, pelvis, femora, and ribs showed no evidence of malignant disease Nine months later, there was no local return of the tumor and the patient felt entirely well The blood pressure remained markedly elevated, and the urine normal In April 1930 he died suddenly at home, probably from cerebral hemorrhage No autopsy was obtained

Case 5 J D a male, aged 69 years, entered the hospital with a history of anorexia weight loss, and urinary retention Cystoscopic examination revealed cystitis and bladder calculi The patient developed uremia from which he died At autopsy, a carcinoma of the prostate with extensive metastases was found In addition there was present a plasmocytoma of the thyroid This tumor measured 1 4 cm x 0 9 cm x 0 9 cm It had metastasized to the regional lymph nodes but not elsewhere

Discussion

In Case 1, a plasmocytoma of the tonsil was removed eight years before generalized bone involvement could be detected For fully seven years the patient showed no signs or symptoms which could be attributed to bone lesions yet during all this time the process was spreading through the lymphoid system as was proved by successive lymph node involvement, and eventually bone lesions characteristic in all ways of multiple myeloma made their appearance

The histology of the several lymph nodes removed and of the bone tumor at autopsy was identical Each showed a plasmocytoma There would seem to be no doubt but that the plasma-cell tumor arose in the tonsil, spread through the lymphatic system, and finally reached the marrow We have been unable to find in the literature any analogous case

In Case 2 it is difficult to say positively whether the lesions appeared first in the bones or in the lymph nodes That an enlargement of a lymph node first brought the patient to the hospital is apparent Symptoms compatible with classic multiple myeloma – in this case, pains in the hip – had been present for some time, and while Roentgen rays did not demonstrate any lesions until later, it is quite possible, and in fact, likely, that they were present when the patient first presented himself at the clinic Our experience with both malignant lymphoma and metastatic carcinoma would lead us to believe that bone lesions may exist for some time before they are detectable by Roentgen ray The initial tumor in this case was a plasmocytoma Cervical lymph nodes became involved a retroperitoneal mass of considerable size developed, and the bone changes though at first considered more characteristic of metastatic carcinoma, later were judged consistent with multiple myeloma

While it was impossible to obtain a specimen from a bone for pathologic examination the absence of any evidence of carcinoma together with the presence of a rapidly growing extraosseous plasmocytoma makes it reasonably certain that the case was one of multiple myeloma with widespread extraosseous involvement

In Case 3 the tumor was again a plasmocytoma, but no metastases were observed either in the bones or elsewhere. The tumor would seem, therefore, to have been relatively benign It should be remembered, however, that eight years elapsed in the first case before osseous involvement was detected

Case 4 presented a plasmocytoma arising from the gum and later involving the alveolar process The histology of the tumor was identical with that of the other cases Radiation and excision caused temporary cure, but the patient died several months later, presumably from cerebral hemorrhage No evidence was at hand that there w

In Case the prostate, the plasmocytoma wh in the thyroid was a purely accidental finding at autopsy The plasmocytoma had metastasized to the regional lymph nodes but to no other region

It is interesting to note that 2 of our 5 cases of plasmocytoma were primary in the thyroid In Hellwig's series of cases, he cites 2 in which the tumor was primary in the thyroid The final outcome of these cases was not described Voegt, who described 1 of these, mentions that x rays of the skeletal system showed no evidence of tumor and that the urine was negative for Bence-Jones protein. The other case, reported by Smith and Shaw, showed no bone involvement by x ray, and one year after removal of the tumor, showed no evidence of recurrence

Treatment

Hellwig states, in regard to treatment, that as long as a plasmocytoma is localized and confined to soft tissue, a clinical cure may be obtained by surgical removal or irradiation or a combination of the two However, if a tumor has locally invaded bony structures or has spread to lymph nodes or to the skeleton, no known therapeutic measure has prevented a fatal outcome We should like to add that irradiation often gives marked relief from pain if the tumor has invaded surrounding structures

Prognosis

The prognosis is most uncertain The course of the disease in Case 1 illustrates this Following removal of the plasmocytoma of the tonsil, the patient remained apparently perfectly well for five years He then had a recurrence of the tumor in his tonsil and also tumor appeared in his cervical nodes It would seem, then, from our own experience and that of others, that the prognosis should be always guarded While a tumor may appear to be slowly growing and an apparent cure may seem to have been obtained by appropriate treatment, the danger of recurrence or development of metastases several years later is great

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PLASMOCYTOMA OF TONSIL.

LYMPH NODE FROM SAME CASE 9 YEARS LATER

VII
Endothelioma

Endothelioma as one form of primary tumor of lymph nodes has been frequently described and numerous reports of such cases have appeared. The textbooks give brief descriptions of such tumors. However, neither Callender nor Gall and Mallory in their classification of tumors and tumorlike conditions of lymph nodes describe endothelioma as a primary tumor. We agree with Ewing and Willis that such a diagnosis, unless confirmed by a complete autopsy, should not be made. The difficulty lies in the fact that metastatic carcinomas, especially those arising in the nasopharynx, present all the characteristics considered by many authors as typical of endotheliomas.

One group of cases that appear to be unquestionably primary endotheliomas of lymph nodes are those described by Bonne in Java. According to this author, there is an extraordinarily high incidence of primary cervical lymph node tumors in the Far East, these tumors being among the five commonest types of all malignant tumors. He further states that out of 265 cervical lymph node tumors without a primary source, he found 119 to be of reticulo-endothelial origin.

Bonne divides such tumors into two types. One, composed of more or less round cells, shows abundant reticulum, the fibers surrounding the cells. To this type of tumor he applies the term "retothelial sarcoma." This tumor apparently corresponds to reticulum-cell sarcoma. The other type of tumor described by him consists of pale syncytial cells, the nuclei containing prominent nucleoli and little chromatin. Instead of growing diffusely, the cells form well-defined strands of tumor tissue with unaltered lymphoid tissue between, giving the impression of a metastatic carcinoma. Reticulum is either absent or present in small amounts. Bonne terms these tumors 'reticulo-endotheliomas' or 'retotheliomas,' since they would appear to represent true endotheliomas derived from the reticulo-endothelium. He states that there are transitions between the two types. He finds that all these tumors are malignant and has seen metastases in the thoracic lymph nodes, liver, and elsewhere. In their terminal stage, they cause necrosis of the skin and large fungating tumors in the neck.

In our series of tumors of lymph nodes we have never encountered a case where the diagnosis of endothelioma could be confirmed at autopsy.

We are in complete agreement with Willis's statement that "endotheliomata" should be tolerated neither as a clinical nor as a biopsy histological diagnosis; only a complete autopsy demonstration of the absence of an occult primary carcinoma justifies the adoption of this diagnosis."

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